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ARCHIVES OF NEUROLOGY AND PSYCHIATRY

FROM THE
PATHOLOGICAL LABORATORY
OF THE
LONDON COUNTY ASYLUMS,
CLAYBURY, ESSEX.

EDITED BY
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PREFACE

THE publication of this volume has been somewhat delayed owing to various circumstances, but principally on account of a printers' strike; in consequence a considerable amount of pathological investigation has been published in journals with a wide circulation in the form of lectures, addresses, and communications by myself to various learned societies. The Pathological Laboratory recently issued in the form of a volume a number of collected papers which had been published in various scientific journals other than the 'Archives' of the Laboratory, and it was intended to issue a second volume of a similar character, but after consultation with the Pathological Sub-committee it was decided that it would add to the value of Volume V of the 'Archives of Neurology and Psychiatry' if it contained the records of all the work carried out in the Laboratory since the publication of the last volume; consequently this volume comprises a considerable amount of work which has been already published. As heretofore, theses for the Doctor of Medicine Degree by medical officers engaged in the asylum service of the London County Council and by gentlemen working in the Pathological Laboratory are contained in this volume. By publishing these theses and other papers by medical officers in the service in the 'Archives of Neurology and Psychiatry,' it is hoped that the attention of the authorities may be called to the fact that they have in their service officers who can find time to pursue clinical and pathological investigation, and at the same time perform in a satisfactory manner the routine duties of their office.

In previous volumes the influence of alcohol and syphilis in

the production of insanity has been discussed very fully, and this volume contains the last of a series of contributions on syphilis in relation to feeble-mindedness. There is still a good deal of work to be done in relation to the influence of congenital syphilis to feeble-mindedness in the light of modern research. It is now generally and widely recognised that syphilis, both acquired and congenital, plays a prominent *rôle* in the production of acquired nervous and mental disease.

Having thus dealt with the two most important acquired conditions producing insanity there still remained the inborn factor to be considered. In two lectures dealing with heredity and insanity the facts deduced from the investigation of over 2400 relatives, who are at the present time, or who have been, in the London County Asylums, are considered. One very important fact has been established, and that is the "Law of Anticipation or Antedating," which was predicted by Morel. I have found, in 420 pairs of parent and offspring, only one instance in which the first attack occurred in the offspring at a later age than in the parent. In over 50 per cent. of the instances the offspring became insane twenty-five years earlier than the parent. A considerable proportion therefore of the insane offspring of insane parents are congenital imbeciles or become insane in adolescence. There is an intensification of the mental defect, and if Nature were left to itself it would tend spontaneously to eliminate all such weak types, and thus there would be either a complete destruction of an unsound stock or a tendency to regression to the normal after three generations, unless there be consanguinity or introduction of unsound elements by marriage into an unsound stock. It may be presumed that there is a tendency of insane germinal determinants to coalesce, or, metaphorically speaking, to crystallise out of an unsound stock. This affords an explanation, hypothetical though it may be, why only one, or perhaps two—seldom more—children of an insane parent become insane. In insanity, as in bodily disease, there are always two factors, viz. the soil and the seed, the inborn and the

acquired environmental. There are individuals born of sound stocks that no acquired conditions, *e.g.* disease, drink, poisons engendered within the body or taken in from without, head injuries, emotional shock, distress, and even profound misery and destitution combined can render insane. There are others, and these are generally from a neuropathic stock, whose mental equilibrium may be disturbed by any one of these conditions or even without any apparent cause, except the physiological conditions appertaining to the function of the sexual glands at puberty, the puerperium, and the climacteric period of life. Between these two extremes are all gradations of mentality from the congenital imbecile and the insane adolescent at one end of the scale to the potential sound mind that no combination of acquired conditions can render permanently insane.

I desire to express my thanks to my assistants, Dr. Candler and Mr. Mann, for the assistance they have given me in correcting the proofs of this volume.

FREDERICK W. MOTT.

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APPENDIX OF COLLECTED PAPERS

- (1) The Oliver-Sharpey Lectures on The Cerebro-spinal Fluid, by F. W. Mott, M.D., F.R.S., F.R.C.P.
(Reprinted from the 'Lancet,' July 2nd and 9th, 1910.)
- (2) The Huxley Lecture on The Hereditary Aspects of Nervous and Mental Diseases, by F. W. Mott, M.D., F.R.S., F.R.C.P.
(Reprinted from the 'Lancet,' October 8th, 1910.)
- (3) A Lecture on Heredity and Insanity, Royal Institution, by F. W. Mott, M.D., F.R.S., F.R.C.P.
(Reprinted from the 'Lancet,' May 13th, 1911.)
- (4) The Comparative Neuropathology of Trypanosome and Spirochæte Infections, with a *Resumé* of our Knowledge of Human Trypanosomiasis, by F. W. Mott, M.D., F.R.S., F.R.C.P.
(Reprinted from the 'Proceedings of the Royal Society of Medicine,' November, 1910.)
- (5) *a.* The Clinical Study of Amaurotic Idiocy (Tay Sach's Disease), by H. B. Carlyll, M.D. Cantab.
b. The Microscopic Examination of the Central Nervous System in Amaurotic Idiocy, by F. W. Mott, M.D., F.R.S., F.R.C.P.
c. The Chemical Examination of the Brain in Two Cases of Amaurotic Idiocy, and Comparison with the Normal Brain, by S. A. Mann.
(Reprinted from the 'Proceedings of the Royal Society of Medicine,' March, 1911.)
- (6) Motor Localisation in the Brain of the Gibbon Correlated with a Histological Examination, by F. W. Mott, M.D., F.R.S., F.R.C.P., E. H. J. Schuster, M.A., D.Sc., and C. S. Sherrington, M.D., F.R.S.
(Reprinted from the 'Proceedings of the Royal Society of Medicine,' B., vol. lxxxiv.)
- (7) The Incidence of Gall-stones and of Primary Carcinoma of the Gall-bladder and Biliary Passages in the Insane, by J. P. Candler, M.A., M.D. (Cantab.), D.P.H.
(Reprinted from the 'Proceedings of the Royal Society of Medicine,' February, 1911.)

Congenital Syphilis and Feeble-mindedness.

By F. W. MOTT, M.D., F.R.S., F.R.C.P.

IN the evidence which I gave before the Royal Commission on the Care and Control of the Feeble-Minded, I expressed the opinion that "syphilis is an active agent in the production of congenital weakness and the degeneracy that accompanies it." Moreover, I was of opinion that "the measure of the effects of syphilis in the production of feeble-mindedness and epilepsy should not be estimated only by those cases in which there are visible and characteristic signs of syphilis on the body." I gave reasons and cited a number of cases in support of this statement.

It is a very important question to decide whether congenital syphilis is a cause of arrest of development of the brain (apart from its causing gross syphilitic lesions) either by the influence of a chemical toxin or some failure of sufficiency of a bio-chemical substance upon the developing embryo. We know that infantilism and various forms of premature decay of the nervous system, which Fournier has termed "parasyphilis," may arise in the children of syphilitic parents, and that these children may not show any gross lesions of a syphilitic nature. The question of the arrest of development of the most complex and highly differentiated tissue of the body is difficult to answer by anatomical investigation, and the bio-chemical changes which we know occur in the blood and tissues as a result of the invasion of the body by the syphilitic organism are not yet sufficiently understood to allow of more than a hypothetical speculation as to the influence they might exercise upon the development of the cerebral neurons.

Until the introduction of the Wassermann reaction we were only able to obtain information as to the existence of a syphilitic taint by statistical and clinical evidence—a not altogether satisfactory source of knowledge, for the reason that the "personal equation" is so frequently biassed and prejudiced that an over-estimate or under-estimate is arrived at according to the pre-conceived idea of the investigator. Moreover, a clinical investi-

gation that is not thorough and accompanied by a personal investigation of the parents, a careful inquiry concerning the result of conceptions, and the search for syphilitic signs or symptoms in living offspring other than the patient, will, as my experience in the investigation of the family history of a large number of cases of juvenile general paralysis shows, lead to a very erroneous idea of the effects of the syphilitic taint. I am afraid that those English authorities who have given such an exceedingly low percentage of imbeciles with a congenital syphilitic taint have not taken the same care in investigation as the German authorities. That the much higher percentage of the latter is probably correct has recently received confirmation by the investigation of the blood-serum of the inmates of imbecile and idiot asylums by the Wassermann method.

Before, however, discussing this subject *in extenso* I will give a brief *résumé* of the evolution of our knowledge of congenital syphilis, especially in relation to diseases of the nervous system.

In the middle ages, soon after syphilis had been introduced into Europe, Paracelsus asserted that syphilis was in the blood, and a pathogenic substance was transmitted to the foetus in conception. Congenital syphilis was described by Ambroise Paré, who in 1633 wrote: "Souvent on voit sortir les petits enfants hors le ventre de leur mères ayant cette maladie, et tôt après avoir plusieurs pustules sur leur corps; lesquels estant ainsi infectés baillent la verole à autant de nourrices qui les allaitent." Astruc and Boerhaave accepted the existence of hereditary syphilis, but owing to the influence of John Hunter's teaching this doctrine fell into disrepute until the facts of hereditary syphilis were established and placed upon a firm foundation by the works of v. Bäreusprung, Wagner, Colles, Virchow, Fournier, Hutchinson, Barlow, Bury, and others. The two last-named authors state: "It may, indeed, now be said in contrast to the early views, that nearly every variety of nervous affection of acquired syphilis has its parallel amongst congenital examples; albeit there are indications of a few broad differences which may be made out as to relative frequency alike of lesions and symptoms between the two groups." Curiously enough, Sir Jonathan Hutchinson, in his article on "Hereditary Syphilis," 'Twentieth Century Practice of Medicine,' devotes only nine lines to the diseases of the nervous system, and he states, moreover, "It has never occurred to me in any single instance to identify the subject of this inheritance in a sufferer from tabes or general paralysis." This is remarkable, seeing the enormous number of cases he must have seen: it differs greatly from the experience of another great

syphilodologist, Fournier. Tabes is very rare, but 2 per cent. of the cases of general paralysis dying at Claybury Asylum during the last twelve years have been of the juvenile form and due to congenital syphilis.

It seems to be proved that syphilis acquired in infancy after birth may be followed by the same results as its acquisition *in utero* or its sperm or germ inheritance. Welander, of Stockholm, records the case of a boy who had acquired syphilis from his nurse when three months old; at the age of thirteen he suffered with interstitial keratitis and nodes; moreover, the teeth were characteristic. Endlitz has also recorded a case of a male child who at the age of two months acquired syphilis from his mother, who had herself been infected by a nursing; at the age of twenty-three he was shown at the Paris Society of Dermatology: he was small in stature, beardless, and with infantile genital development and characteristic teeth. He had been under Fournier's care for cerebral syphilis. In an overwhelming number of cases of congenital syphilis the transmission of the disease to the offspring is directly attributable to the father. The woman in the majority of instances is infected by the man before conception or in conception, so that the child in such cases may acquire the virus both from father and mother. This is termed mixed transmission. In such conditions the offspring is more likely to be infected than when only one parent is syphilitic. According to Fournier, the transmission of the disease occurs in 92 per cent., and the mortality of the offspring is 68·5 per cent.

Colles's law.—A woman conceives by a syphilitic husband without becoming herself infected; the foetus is then only syphilitic by the father, but the mother may subsequently acquire the disease from the syphilitic embryo *choc en retour*; this, however, does not necessarily follow, for the offspring may be syphilitic and the mother escape; moreover, although she can suckle her syphilitic offspring without acquiring the disease, yet if a healthy wet-nurse suckle the child she will acquire syphilis. The usual explanation of these facts is that the mother, by gradual increased doses of the toxin from the syphilitic embryo in its development, has acquired an immunity.

Neisser, however, from his experiments and observations, claims that Colles's law should be re-stated as follows: Mothers of congenital syphilitic children are not healthy and immune, but they are as a rule latent-syphilitic, and in consequence, *apparently* immune. He supports this conclusion by the following facts.

1. The researches of Bauer, Engelmann and Rietschl show that all mothers of congenital syphilitic children give a positive Wassermann serum reaction.

2. The researches of Knöpfelmacher and Lehndorf show that those women who have given birth to congenital syphilitic children within four years react positively in the same

percentage as latent syphilitics. Consequently, in spite of *apparent* health, the mothers of congenital syphilitic children are much more frequently syphilitic than has been supposed.

3. The passage of reaction bodies to a healthy mother can only be a passive one, and the positive reaction would rapidly disappear from the blood of the mother after birth of the syphilitic child if their source were the syphilitic fœtus, but it persists for years.

4. Bauer, Wechselmann and Neisser have shown that there may be a positive serum reaction in the mother and a negative of the child.

5. A series of cases have been published by Halberstädter, Müller. and Reichel, in which the child at birth showed a negative reaction, and only gave a positive reaction when there were definite objective signs of syphilis; in these cases we can exclude passage of the reaction bodies from the fœtus to the mother.

6. The researches of Neisser upon apes afford no support to the occurrence of a true immunity in syphilis.

Another condition which I have frequently met with is that the father and mother are at first both healthy and have healthy children; then, during a pregnancy or absence from home, the husband goes astray and acquires syphilis. The result of married life is that there now occur a series of miscarriages, still-births, dead children, and diseased children. The following case illustrates this: A man, aged 48 years, a ship's steward, was married in 1872, and had a healthy male child in 1873. In 1874 he went away for a voyage and remained away for three and a half years; in 1876 he had a hard chancre. He returned home in 1878, and in 1878 and 1879 his wife had three miscarriages; in 1880 a child was born dead; subsequently four healthy male children were born. Sixteen years after the primary infection the man developed tabes. So far as the records go these last four children were healthy, but it is quite probable that an examination of the blood by the Wassermann test would have shown that they had been affected by the parental syphilis. Any one of these might later in life develop a parasyphilitic affection.

But under some circumstances it may happen that the woman is infected while she is already gravid with a healthy embryo; but the syphilitic husband's sperm does not necessarily infect the developing embryo; the mother may, however, be infected directly from the primary sore or from secretions, and in rare cases the child may then be born healthy, but immune to the disease, for it can be suckled by the syphilitic mother or syphilitic wet-nurse without contracting the disease. This is termed the "law of Profeta." Children born of syphilitic parents are said to be always immune against syphilis; this, however, is disproved by the fact that congenitally syphilitic subjects occasionally acquire syphilis in later life. I have seen several instances, one in particular, which I got Sir Jonathan Hutchinson to see. It was the case of a young man admitted to Charing Cross Hospital; he had typical notched central incisors, saddle-shaped

nose and rhagades at the corners of the mouth. There was a history of chancre, and when he came to the hospital he had a well-marked secondary eruption on the chest and abdomen, which was cured by mercury.

Finger, Ogilvie and others have published exceptions to Colles's law, cases where the mother contracted chancre of the nipple by suckling her syphilitic offspring. But the experimental inoculation of the mothers of syphilitic children by Finger and Neisser with negative results favours this law of immunity; moreover, it accords with Fournier's experience, for he states that he has never seen a case of exception to Colles's law. Moreover, Sir Jonathan Hutchinson says: "My own experience does not supply me with a single exception to Colles's law." From more recent researches we have seen, however, that Neisser concludes that the *mother* is *apparently* immune in Colles's law, and the child *apparently* immune in the case of Profeta's law. In both instances it is latent syphilis rather than immunity.

There is a good deal of evidence to show that infection often takes place by the semen. Hochsinger records observations on seventy-two families in which there was paternal syphilis, but the mothers showed no signs of syphilis during periods of four to nineteen years, although they were repeatedly examined (fifty cases were under observation for more than six years). The seventy mothers gave birth to 307 children—110 still-born, 166 syphilitic, and 31 healthy. The healthy children were all the last born except in four cases. I have met with many cases of undoubted congenital syphilis with most pronounced and unmistakable stigmata in which the mother has never suffered in any way, nor did she show any sign or give any history of infection. It might be argued that these mothers were really the subjects of *latent* syphilis. But why should it be latent in the mother and active in the children? The following is an extremely interesting example illustrating this fact:

E. H—, aged 34 years, came to Charing Cross Hospital, accompanied by her elder sister. She complains of pains in the limbs; she is very deaf, especially on the left side. She has typical Hutchinsonian teeth. Her sister also has typical notched pegtop-shaped central incisors and old keratitis. The sister, a married woman, gives the following history: Her mother had three premature births, then two children born dead, then one which lived sixteen months. She came next, and the patient, E. H—, was born a year later. The married sister also informed me that she herself had had but one child, which was a delicate infant; it had snuffles and died at the age of six weeks. The patient, E. H—, has been

paralysed in the left side since early infancy. It was discovered only by her not being able to walk or use the hand. When quite an infant she had a rash on the skin and the eyebrows came out. Later in life it was noticed she was deaf in the left ear. The left arm and leg are wasted, and the bones smaller. She has no contracture. There is a triceps contraction and marked patellar clonus, but no ankle clonus. This was undoubtedly a case of congenital syphilitic brain disease causing hemiplegia. The mother came to see me and said that she had never ailed in any way, and I could find no evidence of syphilis on the body. The family history is the specially interesting feature in this case, as showing the effects of acquired syphilis upon the offspring, and also the possibility of transmission to the third generation.

Seeing that Levaditi, Bab, and others have seen spirochaetes in the ova, it is possible that the syphilitic contagion may remain in a resting intracellular stage; but when the ovum escapes and is fertilised the syphilitic virus again becomes active, although its virulence is greatly modified and attenuated. This transmission to a third generation is a mere supposition unless, however, we can be absolutely certain that the father was not syphilitic. I could, however, obtain no history of syphilis from the father in the case above recorded. It is no more physically impossible to admit infection of the segregated germ-cells of the next generation than infection of the sperm-cell. It may be observed that Sir Jonathan Hutchinson is most sceptical of transmission; he says—"Nor have any facts been placed upon record which are worthy of much attention as supporting the belief referred thereto." An excellent critical summary of cases has been given by Dr. G. Ogilvie.

In vol. ii. of the 'Archives of Neurology' I pointed out the very much greater incidence of sterility, miscarriages, still-births, dead and diseased children in female tabetics and paralytics than occurs when the male is affected by these diseases. As a general rule when the married woman is the subject of tabes or general paralysis she has been infected by her husband, so that the germinal plasm of both parents may be affected by the virus, but probably this is not so much the cause of the destructive effects on the offspring as the influence of the syphilised maternal blood and lymph, and the constant opportunity during pregnancy of the invasion of the foetal tissues by the specific organism. In fact, the foetal tissues, judging by the readiness with which spirochaetes can be found in them as compared with adult tissues, offer a specially favourable soil for their development.

Table showing the Birth- and Death-rate of Offspring of Male and Female Tabetics and Tabo-paralytics.

	Children alive.	Born alive, but died in infancy or afterwards.	Born dead.	Miscarriage.
Twenty-two married females suffering with tabes or tabo-paralysis; seven of these were sterile.	10	10	18	31
			49	
Fifty-four married males suffering with tabes or tabo-paralysis	151	75	52	

Mendel found that of 252 married female tabetics, 32.9 per cent. were childless. My inquiries regarding the results of conceptions in syphilitic parents illustrate the following points. The usual history is either complete sterility, or miscarriages, abortions, still-births, children dying in infancy of convulsions, marasmus, meningitis, or hydrocephalus; then there may follow children who are *apparently* healthy, but who in later life develop *syphilis hereditaria tarda*, manifested often by interstitial keratitis, nerve-deafness, bone, skin and visceral lesions. The children may be stunted in growth and show obvious stigmata of congenital syphilis, in the form of Hutchinsonian teeth, saddle-shaped nose, and linear scarring around the angles of the mouth. At puberty it may be noticed that the genital organs remain infantile in development, and microscopic observations which I have made on the sexual glands in such cases show atrophy or degeneration of the germ-cells; in the case of the male organ an absence of the spermatozoa; in the case of the female a failure of development of the ova and a great diminution in numbers. This infantilism is frequently associated with various grades of idiocy or imbecility. Congenital syphilitic children presenting those well-determined stigmata may subsequently develop juvenile general paralysis, tabo-paralysis, tabes, primary optic atrophy, epilepsy, chorea, hysteria and meningitis. But it is more common to find *apparently healthy* children born of syphilitic parents subsequently, about puberty or adolescence, developing the various nervous affections mentioned above. It seems as if the virus, as it becomes attenuated, is delayed in its destructive effects, and numbers of family histories I can cite show as a general rule, but by no means invariably, that as the virus becomes attenuated the conceptions may result eventually in healthy children, who in later life manifest no visible signs or symptoms of the disease. But, as

Fournier remarks, the birth of healthy children is "no free pass" for future offspring, and the following cases illustrate this fact :

F. C—, aged 11 years, suffering with blindness since he was seven years old, was brought by his mother to Charing Cross Hospital ; she said the child had had snuffles at birth. There was no family history of nervous disorder or insanity. Three years elapsed after marriage before a seven-months still-birth occurred, then (1) a girl was born that died with fits at one year and nine months ; (2) a girl, living, quite healthy ; (3) a girl, living, quite healthy ; (4) *the patient* ; (5) *boy, aged 9 years*, with paralysis ; (6) *boy*, who suffers with fits. The patient when brought to me exhibited no external signs of syphilis on the body and no evidence of visceral disease. There was slight evidence of paresis of the lower face muscles of the right side, and the tongue on protrusion deviated to the right. There was optic atrophy in both eyes, also cycloplegia and iridoplegia. The fifth was a boy, aged 9 years, and I found him to be suffering with left facial nerve paralysis ; the paralysis came on when he was aged 6 months. The eye could not be closed, nor the forehead wrinkled ; the mouth was drawn to the right, but not markedly. There was no deafness ; he could hear a watch equally well in either ear and at a normal distance. This was probably due to a syphilitic affection of the facial nerve. The sight was now becoming defective in the left eye, the disc being pale with a sharp edge, and probably he will become blind like his brother. The practitioner who sent this patient to me treated the mother for acquired syphilis. The history seems to point to the fact that the treatment by mercury for some time led to the birth of two healthy children (2 and 3) ; it was then suspended, and three children, including patient, were then born, all of whom were seriously affected.

In the following case there was no history of the mother having been treated for syphilis.

Girl, aged 14 years, was admitted to Claybury Asylum suffering with juvenile general paralysis, with well-marked signs of congenital syphilis, viz. notched teeth, rhagades around mouth, saddle-shaped nose. History : No insanity, direct or collateral. Father died of an accident, aged 46 years. History from mother : Mother was married at twenty, father at twenty-two. There were twelve children as follows : (1) dead, 5 months fœtus ; (2) dead, 5 or 6 months fœtus ; (3) dead, 6 or 7 months fœtus ; (4) dead, 7 months fœtus, lived eight hours ; (5) born alive, very frail and delicate, ulcers on legs, inflammation of eyes ; (6) patient ; (7) girl, living, well, aged 16 years ; (8) boy, living well, aged 14 years ; (9) boy, living,

well, aged 12 years; (10) boy, died of *convulsions*, aged 11 months; (11) girl, died at 8 months of *brain disease* and *club foot*; (12) boy, living, well. The patient was an intelligent girl and passed the seventh standard at twelve years old; developed signs of general paralysis and progressive dementia at fourteen and died three years later of this disease. It will be seen that 7, 8, 9 are living and well, then follow two children with nervous affections and death.

As a contrast to the above two cases I may mention the following case. R. D—, a carpet planner, was admitted into Charing Cross Hospital under my care, suffering with well-marked signs and symptoms of tabes. He gave the following history of conceptions following his marriage at twenty-two, which was just two years after he had contracted syphilis with a hard chancre, for which he was treated with mercury for only two months. The first child was born within one year of marriage and is alive and well; he has had six healthy living children, one of whom died, aged 9 years; there were also twins. Why was the wife not infected? Had she inherited immunity? These are questions which might well be asked in respect to this case. Healthy children are occasionally born between diseased children; as we have seen above this may be sometimes accounted for by treatment of the mother.

Hochsinger throws doubts upon a healthy child slipping in between diseased children. Until the introduction of the serum reaction we had no means of knowing whether a child of syphilitic parents was free from taint, for although we are unable to see any external signs of disease yet the internal organs may be extensively diseased, and the following case illustrates this fact most conclusively.

A. R—, male, aged 22 years, was admitted to Claybury Asylum. He was an able-bodied seaman, but had been invalided on account of fits. There were no external signs of syphilis on the body. There was a history of his father having died of general paralysis in Banstead Asylum, and of a brother, a weak-minded imbecile, being at that time in Caterham Asylum. Whereas the patient, A. R—, presented no external signs of syphilis, his imbecile brother had the characteristic nose and teeth. A few days after admission to Claybury he had a succession of epileptiform seizures; his temperature rose to 108.2° F.; the temperature was reduced by cold sponging, but he never regained consciousness, although the convulsions ceased upon the administration of chloral. The case turned out *post-mortem* to be a typical case of general paralysis. Although there were no external signs of syphilis, the liver showed an extraordinary condition.

It weighed 1200 grm.; the left lobe consisted almost entirely of nodules varying in size from a pea to a marble united to one another by dense bands of fibrous tissue. The right lobe was also nodular in places, and the capsule was here and there thickened so that portions of the organ were partially separated. Microscopic examination showed perihepatitis and extension of the dense fibrous tissue along the vessels and bile-ducts. There was nodular fibrosis of the aorta, otherwise no signs of visceral syphilis was discovered.

Max Nonne believes that it is not impossible for a healthy child to slip in between two unhealthy ones. He states that within the last few years a large amount of material precisely controlled and obtained from the Engel Reimer division of the Hamburg Hospital (St. Georg) has shown that not infrequently such a thing happens.

I have met with numerous cases in which the mother has had a series of healthy children, followed by miscarriages, still-births, and children dying in infancy followed by syphilitic and parasyphilitic children. These cases often show the necessity of a systematic inquiry of the results of every conception, for the following case of juvenile general paralysis and optic atrophy was shown to me as a case in which syphilis could be excluded as there was a large healthy family and no history of syphilis of the parents; yet a systematic inquiry showed clearly that the reverse was the case, and in spite of the denial of the father that he had suffered with venereal infection, and of the mother that she had ever suffered with any signs or symptoms which could be associated with acquired syphilis, the history clearly points to maternal infection after she had had a family.

A. B—, was a bright, intelligent girl, who passed the sixth standard of the board school and gained several prizes. She left school at thirteen; her periods never came on, and this was the assigned cause of her complaint in the notes received from the infirmary, where she was diagnosed as an imbecile due to congenital brain disease. I took the following notes on the case: She is now aged over 15 years; she is completely blind in both eyes, she is quite childish, but will talk and answer questions, but in the manner of a little girl of six or seven. She has no delusions or hallucinations, is obedient and now takes her food, although on admission to the asylum she was noisy, crying and troublesome. She was sent as an epileptic, but she has had no fits while in the asylum. Apparently, from what the mother tells me, she had several fits (like fainting attacks) while in the infirmary. She sits in a chair all day; the legs are rigid and semi-flexed, the knee-jerks are not obtainable. She continually fidgets with her

hands. I observe only slight tremor of the lips and tongue. The pupils are of medium size and do not react to light. There is primary optic atrophy on both sides. She has never complained of headache and there has been no vomiting. She does not respond to the calls of nature and passes urine and fæces unheeded. She recognises her friends when they come to see her and talks to them affectionately. Her palate is high and narrow; the teeth show no signs of congenital syphilis, nor were there any stigmata on the body observed by the medical officer on examination; syphilis was not therefore suspected. I interviewed the father and mother. Both said there was no insanity or nervous disease on either side. The mother informed me that she had had fourteen pregnancies. The patient was the next to the youngest living child. Prior to the birth of the patient she had had eight children, all of whom are now alive and grown up and some were married; then she had *two miscarriages followed by twins born dead*, followed by the patient, who had snuffles and a rash on the bottom soon after birth, for which she took her to St. George's Hospital where they gave her grey powders; she did not continue the treatment long. The dementia and paralysis are progressing. This is in all probability one of those cases of the husband acquiring syphilis during the pregnancy of the wife and subsequently communicating the disease to her with the usual result as regards further conceptions.

Again, a long mercurial treatment of the father, although usually protecting the offspring from congenital syphilis, does not give a positively certain voucher of freedom from taint, as the following case shows: An intelligent professional man acquired syphilis; was treated by eminent authorities with mercury for several years; four years after the primary sore he consulted an eminent specialist as to the advisability of marriage: he was assured that there was no danger to his wife or offspring. He waited a year and married, with the following results: The first two children were born alive but died within a day or two of birth; the third developed keratitis and otitis with deafness; this child was seen by specialists, who pronounced the affection to be syphilitic; the fourth developed general paralysis and died with characteristic lesions at one of the London asylums; the last two are now bright and healthy children. The microscopic investigation of this case was ably carried out in the laboratory by Dr. Rondoni. The clinical notes and results of this investigation were published in the 'Proceedings of the Royal Society of Medicine.'

As an explanation it may be surmised that either he infected his wife by his sperm or that this was a case of spermatic infection by the male

without the wife being infected. She had no signs or symptoms of syphilis, but that proves nothing. It is probable that the spirochæte had taken up its abode in the lymphatics of his testicles and had not been destroyed in spite of the adequate treatment he had received for several years.

Sir Jonathan Hutchinson asserts that "a large experience on this point has led to the conclusion that a man rarely becomes the father of a syphilitic child if an interval of two years has elapsed since the disease was acquired." Now we have reason to believe that the specific cause of infection is a living organism and that the testis is not an unusual location of it; moreover, the living organism may remain latent for a long time, consequently the sperm may be infected long after the primary infection, and this may explain the case referred to; likewise if the ovaries are infected it may explain the fact that although the law of gradual diminution of virulence and risk of transmission holds good, yet exceptions may occur, as the following remarkable case reported by Molénes shows: "A woman, aged 44 years, was married at the age of twenty-one to her first husband, by whom after the birth of a still living child she was infected by syphilis. An energetic treatment of husband and wife with mercury and iodide was adopted. In the course of the following years she had six children who all died at ages from eighteen to twenty months with symptoms of meningitis. Six years after the death of the husband she married a healthy widower, father of two healthy children aged respectively 16 and 19 years. She now manifested a recurring syphilitic psoriasis for which she received courses of treatment. Twenty-two years after the primary infection and by her healthy husband she gave birth to a child. This child, just as the former ones, died at the age of eighteen months with symptoms of meningitis (convulsions, vomiting, and coma)." (Max Nonne.)

We may ask the question: Do recent researches and especially the discovery of the *Spirochæta pallida* and the inoculation of animals enable us better to understand the cause of congenital syphilitic disease, and especially the relation of the disease of the parents to imbecility, idiocy, epilepsy, and parasyphilitic affection of the offspring? Also, are we better able to understand and explain some of the anomalous cases of which I have given examples? If it be admitted that the *Spirochæta pallida* always remains a spiral organism and never undergoes any intra-cellular modification, then it becomes very difficult to explain spermatic infection of the ovum, for there is no possibility of the spirochæta being contained in the head of the fertilising spermatozoon; it might, however, be supposed that the spirochæta gains entrance to the ovum during fertilisation or

subsequently. The researches of Leishman on the spirochæte of tick fever suggest the possibility of an intra-cellular phase of the spiral organism and its existence in the form of infective chromidian granules. Moreover, in support of this hypothesis I may mention that Neisser in his experimental investigations on apes has observed that the tissues of infected animals in which no spirochætes were demonstrable could nevertheless be used effectually for inoculation. The spirochæte may be one form of the syphilitic organism, but there may be other minuter stages analogous to the spores of bacilli. Chromidian granules are contained in the *Spirochæta pallida*, and in all probability serve a similar function to the nucleus in more highly developed unicellular organisms; sometimes these chromidian granules can be seen in enormous numbers in tissues where the spirochætes are found. Several observers have seen and described spirochætes in the ovum, and it is improbable that such an infected ovum, even if it were capable of fertilisation and segmentation, would undergo development to an embryo. Consequently in those cases where the mother escapes infection by the parasitic organism and the offspring alone is infected by it there are two possible explanations:

(1) The head of the spermatozoon is infected by a hypothetical, syphilitic chromidian granule which *may* subsequently multiply and produce the syphilitic lesions.

(2) That if the specific organism never undergoes any modification or metamorphosis and only multiplies by longitudinal or transverse fission, the explanation of infection would be that spirochætes contained in the sperm may remain alive in the uterus, and gain ingress to the developing embryo without infecting the maternal uterus.

It has been proved experimentally that the semen may contain the syphilitic contagion, for Neisser and Finger have shown that the testicles of syphilitic monkeys can be used to inoculate the chimpanzee, and a chimpanzee was successfully inoculated by Finger with the semen of a man suffering from secondary syphilis.

In the investigation of the family histories of syphilitic parents I have been struck with the relatively few cases of children who have survived after manifesting in infancy symptoms pointing to brain disease; and this accords with other facts, viz. that although I have been able to collect sixty fatal cases of juvenile general paralysis and tabo-paralysis, I have only met with four fatal cases of coarse syphilitic brain disease due to congenital syphilis. Moreover, when I was searching for juvenile general paralytics I visited Darenth Asylum for Idiots, and I was much surprised at the

relatively few cases Dr. Taylor, the superintendent, could show me of imbeciles or idiot children who presented obvious and obtrusive evidence of congenital syphilis. There were not more than could be counted on the fingers. It is probable, however, that ophthalmoscopic examination would have detected some cases of primary optic atrophy and some case of choroido-retinitis; moreover, a careful inquiry of the mothers regarding the ultimate result of conceptions would (as I have found in quite one half the cases of juvenile general paralysis) have revealed the fact that congenital syphilis may have been a cause of congenital amentia in a certain number of cases in which there are no obtrusive stigmata.

In the London County asylums I have met with a few fatal cases of congenital hemiplegia, epilepsy, and epilepsy with imbecility due to syphilitic endarteritis and softening. I have also met with one case of endarteritis and gummatous meningitis in a congenital syphilitic girl, but relatively to juvenile general paralytics and tabo-paralytics with optic atrophy these cases are very rare. Moreover, I have looked through the 'Revue Neurologique' since its commencement seventeen years ago, and I do not find more than a dozen cases recorded. Max Nonne cites only a few cases, and Still states that he has seen very few cases, and that they are rare as compared with juvenile general paralysis. The reason is doubtless due to the fact that if the *Spirochæta pallida* gains access to the cerebro-spinal cavity the offspring dies either before birth, at birth, or shortly after or within a year or two, the causes of death being given as convulsions, hydrocephalus, or meningitis.

The classical works of Fournier, Hochsinger, Barlow, Bury, and others, have long demonstrated that many serious organic nervous diseases of children are the result of congenital syphilis, and Jullien was able to demonstrate that among 162 living children the progeny of forty-three syphilitic parents (in 206 pregnancies), 50 per cent. were affected with meningitis and convulsive symptoms. Although in my experience these conditions are common in congenital syphilitic infants, few of those so affected survived till puberty or adolescence; it is probable that when the central nervous system is invaded by the organism there is a general *Spirochæte septicæmia* which even the administration of mercury is unable to overcome sufficiently to prevent a fatal termination. The observations of Heubner as to the frequency of affection of structures and organs in congenital syphilis are of interest; according to this eminent authority the structures are affected in the following order: liver, lungs, spleen, alimentary canal, heart and blood-vessels, and lastly the nervous system.

Rumpf gives the relative frequency of affection of the nervous system as 13 per cent. Gasne studied the spinal cords of thirty fœtuses, of which twenty-six were born of syphilitic parents; in four cases he found profound lesions identical to those observed in acquired syphilis, and in seven cases there were doubtful changes. He also observed that the lesions were predominant in the posterior region of the spinal cord.

Ranke, in a very valuable investigation, has studied the brain changes in congenital syphilis. He has made observations upon sixty brains of fœtuses and infants with a view of determining whether in cases of tabes and general paralysis due to congenital syphilis the changes in the central nervous system agree with the lesion of the brain of congenital syphilitic children, or whether the lesions should be attributed to damage of the germ-plasm during development. He first points out that it was necessary to ascertain if the *Spirochæta pallida* be present in the brains of congenital syphilitic fœtuses and new-born infants, and if this be the case whether it can be concluded that the lesions are directly due to its presence. All the organs of the body may show characteristic lesions in congenital syphilis; they may be found in the specific skin-lesions, especially the bullæ of pemphigus, the lymphatic glands, the pancreas, liver, spleen, kidneys, lungs (white pneumonia), the bones, and the vascular system. There are two forms of morbid change in these organs and tissues—viz. exudative, inflammatory—with which also must be associated gummatous neoplasms in the organs of syphilitic children. Besides these changes there is a cell proliferation independent of the vascular distribution, and which has been described as occurring especially in the liver and kidneys. In addition to this evidence of proliferative changes Stroebe, and particularly Karvonen, have described a progressive arrest of development in the kidney as shown by a diminution of the normal glomeruli, and in the presence at the time of birth of pseudo-glomeruli; also there is an appearance of necrogenous tracts of tissue in the parenchyma of the kidney which these observers regard as especially characteristic of congenital syphilis. Ranke remarks that none of the standard text-books on children's diseases deal efficiently with the subject of congenital syphilis and the nervous system, and no mention is made of changes in the central nervous system by Rudolf Hecker in his excellent 'Beiträge zur Histologie und Pathologie der Cong. Syphilis,' 1898.

The cerebral gumma generally associated with progressive meningitis and meningo-encephalitis has been most frequently described, but not infrequently this is associated with disease of the larger cerebral vessels

which was first found in the brain of a syphilitic child. These cases of syphilis of the nervous system will be described later when the symptoms of infantile syphilis of the nervous system are considered.

But in addition to these reported cases of specific affection of the nervous tissues in congenital syphilis, which are indistinguishable in their naked-eye and microscopic characters from similar affections of the adult due to acquired syphilis, a few cases have been reported of arrest of development; especially interesting in this respect is a case of Ilberg's, in which a child, aged 6 days, the subject of congenital syphilis, was found at the post-mortem examination to possess a brain exhibiting a remarkable arrest of development of the centrum ovale, the corpus callosum, and other commissures, as well as of the pyramidal systems of fibres. There was also asymmetry of the two halves of the cerebellum and arrest of development of the optic nerve-fibres. Sibelius has reported changes of a more delicate character; he found in his researches of the central nervous system of congenital syphilitics groups or colonies of spinal ganglion cells exhibiting delayed or abnormal development. In very severe cases of congenital syphilis he was able to demonstrate such colonies of abnormal cells amid typical ganglion cells in abundance and relatively often. He considers these morbid evidences of delay and arrest of development to be occasioned by the syphilitic toxin.

CONGENITAL SYPHILIS AND ARREST OF DEVELOPMENT OF THE BRAIN.

In the light of modern investigations, can congenital syphilis be responsible for the arrest of development of the brain, and the production of various forms of feeble-mindedness? This is a question of great practical importance; the anatomical evidence rests upon far too meagre reports, and when we fall back on statistical and clinical evidence there is considerable diversity between the results of investigation by German and English authorities.

Binswanger, whose statistics have been based upon a large number of idiots, gives 9·5 per cent. as certain, and 12·2 per cent. probable syphilis of one of the parents. Similar results were obtained by Wildermuth. Ziehen gives 10 per cent. demonstrable and a further 17 per cent. probable. On the other hand, Bourneville holds that congenital syphilis is an exceedingly rare cause of idiocy. Langdon Down found it in only 2 per cent. of cases, and Shuttleworth, among 1000 idiots at Darenth, only found 1 per cent. of congenital syphilis. Telford Smith found only eight

cases with marked evidence of congenital syphilis amongst 580 inmates of the Royal Albert Asylum. Similarly, Brown, in America, only found 1-1.5 per cent. of syphilitic origin. Seeing how very prevalent syphilis is among the population, it is impossible to judge how far syphilis on the father's side should be considered as cause or coincidence. On the other hand, we should be considerably under the mark if all cases of arrested development of the brain were omitted that did not exhibit manifest stigmata of congenital syphilis, *e.g.* Hutchinsonian teeth, old keratitis, rhagades at the angles of the mouth, nerve-deafness, onychia, saddle-shaped nose, epiphysitis, infantilism, etc. Quite one half of the sixty cases of juvenile general paralysis which I have notes of showed none of these obvious stigmata, and yet their history showed that they were congenital syphilitics.

There can be no doubt that syphilis in the parents may lead to infantilism in the offspring, and I have seen numerous cases of such in which there were none of the above-mentioned obtrusive signs of syphilis, and yet other children of the same parents presented well-marked obtrusive stigmata; moreover, cases show that one individual of a family of congenital syphilitics may exhibit the characteristic stigmata of congenital syphilis and another show no external signs, yet the internal organs may exhibit post mortem the most marked evidences of the disease. If syphilis can produce bodily infantilism, including arrest of development of the reproductive organs—a not infrequent condition in juvenile general paralysis—surely there is no reason why it should not lead to arrest of development of the most highly differentiated and specialised tissues of the body, *e.g.* the cerebral cortex.

An important piece of evidence has lately been forthcoming in the examination of the blood-serum of idiots by the Wassermann reaction, and I cannot do better than quote the work done by Dr. Dean in the Serological Department of the Royal Institute for Infective Diseases, Berlin. Dr. Dean remarks: "The examination of the blood-serum of idiots by the Wassermann reaction has been the subject of several papers. The French investigators, Ravaut, Breton, Petit, Gayet and Cannac, examined 246 cases, of which 76 were found to give a positive reaction. Kellner, Clemenz, Bruckner and Rautenberg examined 216 cases, of which 13 gave a positive reaction by Stern's method and 9 gave a positive reaction by the original Wassermann method. Lippmann, working in Wassermann's laboratory, examined 78 cases at Uchtspringe and obtained a positive reaction in 7 (9 per cent.). An examination of the cases at the Dalldorf Asylum gave a

result of 13·2 per cent. Lippmann also examined 77 cases by clinical methods and decided that 40·2 per cent. showed signs of congenital syphilis. Dean, working in the laboratory of Wassermann, examined the blood-serum of 330 cases from the Willhelmstift Asylum, Potsdam, and found that 51 cases gave a positive reaction—15·4 per cent. Among the 330 cases were 9, or including the doubtful cases, were 13 which from physical signs or symptoms would have justified the diagnosis of congenital syphilis. Among 13 parents whose serum was examined 9 gave a positive reaction. Cases have been reported by Plaut and others in which the husband or wife of a syphilitic who has never shown any signs of syphilis have nevertheless given a positive reaction. Linser, quoted by Buck, has examined a series of children of syphilitic parents, and finds that two thirds give a positive reaction, while only one third show any other sign of infection. Numerous cases are also on record in which it has been demonstrated that the apparently healthy mothers of syphilitic children give a positive reaction, and conversely the serum test has been positive in apparently healthy children by syphilitic mothers. The numerous investigations on these lines tend to prove that evidence of a positive serum reaction may be accepted even in the absence of the usual signs and symptoms of congenital syphilis. Dean concludes his interesting and valuable paper with the following apposite remark: "It seems to me reasonable to think that many cases of idiocy should be classed with that form of syphilis which manifests itself alone by a selective toxic action upon the nervous system."

Probably a number of unsuspected cases might by the Wassermann reaction show latent syphilis; thus:

Quite recently a female congenital imbecile died in Claybury Asylum, aged 37 years. The brain weighed only 1140 gm.; there was no obvious wasting of the cortex and no thickening of the membranes or granulation of the ventricles. The convolutional pattern was simple. The blood gave a positive Wassermann reaction, but there were no signs of syphilis on the body, although the notes state that while in the asylum the hair had been dropping out. The cerebro-spinal fluid, probably on account of admixture of blood, gave a proportionally weak reaction; there was no lymphocytosis. Remarkable changes in the cortical cells were found, particularly in the frontal lobes, by Nissl, Cajal and Bielchowsky methods. They were similar to, but not so marked or universal, as those found in cases of amaurotic idiocy. Moreover, by Scharlach and Sudan III stains a fatty change was found in these structurally altered cells. Granulation-cells, however, were

not met with, nor was there evidence of any marked glia proliferation—characteristic features of amaurotic idiocy. It is of interest to note that both the ovaries were small, dense and fibrous, and examination of a complete series of sections from each showed no evidence of mature or immature ova. The uterus was small, and there was no evidence of any inflammatory condition to account for the change in the ovaries. A full account of this interesting case will be published later.

Dr. Chislett relates an interesting examination of a whole family. The father, a general paralytic, acknowledged syphilis, and his serum gave a positive reaction. The mother had never to her knowledge had the symptoms of primary or secondary syphilis, but eight years after marriage had a tertiary ulcer on the left leg. There were ten pregnancies; two children were prematurely born, and two died in infancy. The blood-sera of the remaining six were examined. The eldest, a boy of sixteen, was described by his mother as very nervous and stupid as a school-boy; his serum reacted positively although he showed no signs of syphilis. A girl of twelve was deaf in one ear, but otherwise normal; her serum was also positive. A girl of ten had a negative serum; a boy of eight, with rhinitis and conjunctivitis, had a positive reaction, and the two youngest children of six and four years respectively had negative sera.

It is probable that syphilis, therefore, plays a more important part in the production of idiocy and imbecility than is apparent from the English statistics.

Alcoholism.—The influence of syphilis is frequently combined with chronic alcoholism, and the latter among the poorer classes, being a more easily ascertainable cause by those preparing statistics, is assigned as the cause in the parents of the mental deficiency in their offspring. Both poisons co-operate in devitalising the tissues of the body, and there is no reason to suppose that the germ-cells escape from this devitalising influence. Koenig, in a valuable and interesting paper delivered at the meeting of the British Medical Association at Oxford, 1904, gave as his experience at Dalldorf Asylum for Imbeciles and Idiots that “the offspring of paralytic parents are often imbeciles, idiots, victims of infantile cerebral paralysis, sufferers from early epilepsy, chorea, meningitis, congenital syphilis, and various neurotic ailments. There would be a considerably larger number of these youthful invalids but for the high rate of sterility, miscarriages, still-born and short-lived offspring. I have recorded 150 absolutely sterile marriages not including those of a more or less long train of abortions. Among the adult descendants I have noted a fair number

of paranoiacs, cases belonging to the *dementia præcox* group and other types of organic and functional disorder. On the other hand a not infrequent record of exclusively sound children could be obtained. In quite a number of these homologous cases both ascendants and descendants had a clear history of syphilis." With this statement my experience entirely accords. Koenig, moreover, asserts that too much insistence cannot be laid upon syphilis being the necessary step in the production of general paralysis. Alcoholism and environment are contributory factors, but a much greater allowance, however, has to be made for the force of hereditary predisposition in the production of feeble-mindedness in all its forms.

There are reasons for supposing that general paralysis occurs only in a community which has acquired a widespread immunity through generations to syphilitic infection; it is a true type of acquired mental derangement.

Beard, in the discussion on heredity, when Koenig read his paper, said: "It is a known fact that toxins weaken cells and therefore germ-cells; a germ-cell as an adult living organism with a life-cycle must, like all living cells, feed, grow, reproduce, and exhibit irritability." Consequently, we may presume that there is reason for supposing that the two most potent and prevalent poisons, alcohol and syphilis, may, without killing the germ-cells, diminish their *vita propria*, and thus lead to the various disordered and diseased conditions of the nervous system.

Nevertheless, experience shows that imbecility and idiocy are more frequently met with in rural populations than urban; it is a fact even in communities, where purity of living and sobriety are the rule, that imbecility, idiocy, and certain forms of insanity are almost as common as among the general population. Again, in the rural districts of Ireland syphilis is comparatively infrequent and general paralysis is hardly ever seen, yet the relative percentage to the population of imbecility, idiocy, and insanity, is very high. Doubtless this fact, as well as the fact that a greater proportion of cases of congenital amentia *pro rata* occur among the inmates of rural than urban asylums, may be accounted for thus: there has been a constant drain of emigration of the mentally and physically fit to industrial centres, leaving the unfit to procreate their species.

In the large number of cases of juvenile general paralysis which have come under my notice, quite one half have been congenital imbeciles who at puberty or later developed general paralysis. I have not been able to associate the congenital imbecility with a marked mental deficiency in the parents, although I should say in quite 20 per cent. of the cases I ascer-

tained that the father had died in an asylum of general paralysis. The subjects of congenital imbecility bore on their bodies well-marked stigmata of congenital syphilis or exhibited signs of bone or visceral syphilis at the post-mortem examination more often than those who up to puberty were bright and intelligent. The examination of the brains of these congenital imbeciles showed no signs of endarteritis or gross changes to account for the failure of development of the brain. Moreover, the majority of these congenital imbeciles were stunted in growth and their reproductive organs and genitals were infantile. Examination of the ovaries showed great deficiency of ova in numbers and development. The testicles generally were very small and showed no spermatozoa. Moreover, besides the more or less recent degenerative changes in the cortical pyramidal cells, there were many indications of arrest of development. I cannot but think, therefore, there is evidence to show that the syphilitic virus may devitalise the germ-cells and play a more important rôle than has been generally ascribed to it in the production of the various forms of congenital feeble-mindedness. This it may do either by arrest of development of the functionally more complex neurones of the brain; or by inducing a biochemical metabolic instability, it may lay the foundation of functional neuroses and psychoses. These congenital morbid conditions are, then, not due to the direct action of the specific organism upon the brain, but to bio-chemical changes in the developing embryo, changes which may lead to its subsequent immunity, complete, or partial to the action of the specific organism. Possibly the existence of a much greater percentage of imbeciles and idiots which give the Wassermann reaction than can be shown by physical signs pointing to congenital syphilis may be explained in this way.

THE EXISTENCE OF SPIROCHÆTES IN THE CENTRAL NERVOUS SYSTEM.

Several investigators have found the specific organism of syphilis in great numbers in the central nervous system of infants dying of congenital syphilis. Drs. Ravaut and Ponselle found spirochætes in great numbers in the vessel wall, in the lumen of the vessels and inflamed pia arachnoid tissues of a congenital syphilitic infant five weeks old suffering with meningo-myelitis. Ranke examined twelve cases of congenital syphilis in which the infant was born dead or died soon after birth, and in nine he found abundance of spirochætes in the inflamed pia-arachnoid membranes, in the walls of the vessels, especially the veins, and in the lumen of the

vessels; this was associated with characteristic tissue changes in the form of lymphocyte and plasma-cell infiltration, endothelial proliferation and neuroglia hyperplasia and proliferation. Such a condition indicates a spirochæte septicæmia and is inconsistent with life. If the central nervous system is invaded by the spirochæte during gestation or in early infancy death takes place either before birth or shortly after, and if it were not for the fact that invasion of the central nervous system is soon followed in the majority of cases by death, there would be a much larger percentage of nervous diseases due to congenital syphilis. Inasmuch as only 4 to 8 per cent. of adults with acquired syphilis suffer with diseases of the nervous system, the number of cases dying in early infancy of the nervous system is proportionately very high, notwithstanding the fact that there are not very many reported cases with post-mortem examination. Ravaut has contributed an important series of observations conducted upon twenty-eight congenital syphilitic children. He examined the cerebro-spinal fluid every time nervous symptoms were manifested, and found that such symptoms were accompanied by lymphocytosis. He suggests that lymphocytosis of the cerebro-spinal fluid may be used as a means of diagnosis of congenital syphilis when obvious signs are absent; moreover, if anti-syphilitic treatment be adopted the lymphocytes will disappear.

LESIONS OF THE NERVOUS SYSTEM DUE TO CONGENITAL SYPHILIS.

In taking the family histories of a number of cases of juvenile general paralysis and other affections due to congenital syphilis, I have been struck by the fact that the mother frequently stated that following miscarriages and children born dead were children who died in infancy of convulsions, of water on the brain, and of meningitis.

Hydrocephalus.—One of the earliest observers of the relation of congenital syphilis to hydrocephalus and other diseases of the brain producing mental affections was Mendel. He refers to the fact that Carl Haase in the year 1828 related the case of a young woman who was infected by her husband at the age of twenty-two; in consequence she had three premature still-born children; a fourth was born at full term living, but died at the age of seven months of hydrocephalus. He also mentions that Von Rosen, in 1862, published several cases in which the hereditary syphilitic children died of hydrocephalus in early infancy; moreover, Engelberg, Howitz, Cruveilhier, and v. Bärensprung described cases, and Howitz

ascribed to pachymeningitis and leptomeningitis a fatal hydrocephalus in a congenital syphilitic child. Similar cases were recorded by Virchow, v. Bärensprung, Fournier and Mendel himself.

Congenital malformations as well as hydrocephalus may arise from vascular disease in early uterine life. Elsner has described interstitial inflammation of a specific character affecting the choroid plexus. A case was recorded by Dr. Ashby in which hydrocephalus began in a syphilitic infant at the age of three months, and he mentions a case of Heller's in which hydrocephalus came on between the fourth and seventh months. Four cases have been recorded by Sandoz, in which hydrocephalus was present at nine weeks, at six weeks, a few days after birth, and about fourteen days after birth; the first three were examined post-mortem and a thickening and roughening of the ependyma of the lateral ventricles was discovered; moreover, the choroid plexus had an œdematous appearance and was gorged with blood.

This condition is not uncommon; Fournier states that he has met with thirty cases in private practice. Hochsinger has studied 362 cases of congenital syphilis; of these 34 were hydrocephalic; in the majority of cases it began within three to eleven months of birth and it was present six times in foetal life; nervous symptoms were absent in 11 cases, but in others the symptoms were restlessness, sleeplessness, chronic vomiting, contractures and convulsions, increase of tendon reflexes, nystagmus, and idiocy. It may therefore in rare cases closely simulate tubercular meningitis in its symptomatology; in some cases the beneficial effects of treatment have proved its syphilitic nature; examination of the cerebro-spinal fluid would help to determine a diagnosis, also the blood should be submitted to the Wassermann test. Hydrocephalus is usually met with in early life and generally proves fatal when the symptoms are obvious, but Oppenheim mentions that he once saw a case of well-marked hydrocephalus, which first developed obvious symptoms at puberty and subsequently very severe phenomena developed. It is manifest that hydrocephalus is the result of an accumulation of cerebro-spinal fluid in the lateral ventricles; all syphilitic conditions, therefore, which prevent the escape of the fluid from the lateral ventricles, where it is mainly secreted by the choroid plexus, will occasion its accumulation. Still suggests that congenital malformation might cause blocking of the *iter a tertio*, but seeing that Ranke has shown that true syphilitic specific inflammations of the membranes and encephalitic foci are common in congenital syphilis, it is more easy to explain the hydrocephalus by the effect of these lesions inter-

fering with the outflow of cerebro-spinal fluid. Miliary gummata of the ependyma of the lateral ventricles have been described by Virchow and Jürgens in cases of syphilitic hydrocephalus. Fournier points out the practical importance of recognising that hydrocephalus may be a manifestation of congenital syphilis because of the liabilities to infect a wet-nurse. He cites a remarkable case of M. d'Astros in support of his arguments. It would therefore be wise to regard a hydrocephalic infant as *suspect*, and in the light of our present knowledge we are able to decide by the Wassermann reaction of the blood-serum whether the infant should be treated for congenital syphilis. The Wassermann reaction might therefore be tried in all cases of hydrocephalus in which syphilis cannot with certainty be excluded, or the hydrocephalus accounted for by other causes.

All the forms of brain syphilis which occur in the adult as the result of acquired syphilis may occur in infancy, childhood, adolescence, and, in rare cases, even later in life, as the result of congenital syphilis. This is as we should expect now that we know that syphilis is due to a specific organism, which may remain latent in the body for years, to become active when some depressing influence affects the tissues. As pointed out by Wilks long ago, the tissue changes of syphilis are the same in the primary, secondary, and tertiary lesions. The reason that congenital syphilitic disease of the nervous system is not much more common than it is, is because invasion of the central nervous system is usually fatal to the developing offspring while *in utero*, or soon after birth. Another reason is, that congenital syphilis is usually diagnosed and responds well to mercurial treatment. Hutchinson remarks thereon: "Some of our most noteworthy therapeutic triumphs are often obtained when mercury is judiciously employed for infants who are the subjects of syphilitic cachexia; they fatten and thrive under it"; but he also expresses the necessity of caution not to use mercury too vigorously, for he thinks that its improper use in infancy is very injurious to the second sets of teeth. However, this warning need not deter us from administering mercury, for the syphilitic virus is more potent for harm to the enamel germs than mercury.

SYPHILITIC LESIONS OF THE NERVOUS SYSTEM.

True syphilitic diseases of the nervous system in congenital syphilis are nearly always combined; thus we find a generalised leptomeningitis and pachymeningitis, small and large gummata, gummatous neuritis and

endarteritis associated in varying degrees. A certain number of such cases have been recorded, *e.g.* Sir T. Barlow recorded the case of a male infant, aged 15 months, who had weakness of facial muscles and nystagmus. At the post-mortem examination small conical tumours were found in the fourth, fifth, sixth, seventh, and eighth nerves, at their point of exit from the brain stem; these appeared to be of a gummatous nature. There was an associated endarteritis; the basilar and all the vessels of the circle of Willis were extensively diseased; these were opaque, dirty-white in colour, and almost cartilaginous in consistence; the lumen was greatly narrowed by thickening of the interior, and the small arterioles of the pia mater were similarly affected. N. Chiari has recorded a case of endo-meso- and peri-arteritis syphilitica in an infant, aged 15 months, and Bury, Money, Jürgens, and many others have published similar cases. The following case, which was published in full detail in the "Morison Lectures," 'Archives of Neurology,' vol. iv, is of great interest, for it illustrates the fact that a typical congenital syphilitic child may attain a fair degree of intelligence, and then, owing to a latent virus becoming active, at puberty suffer from a universal and progressive gummatous meningitis and endarteritis.

E. M. A—, female, aged 16 years, admitted to Claybury Asylum August 30th, 1905, died July 8th, 1906. Her mother had three miscarriages, then five children born alive, of which she was the last. She was delicate from birth; she had snuffles and coryza, and was treated with grey powder; she was undersized, looking about eleven years of age, and had well-marked Hutchinsonian teeth; she must have been fairly intelligent, as she was in the sixth standard at the board school. On admission she was thought to be a congenital imbecile suffering from mania. Her conduct had changed, she sang snatches of music-hall songs, and played with dolls like a child of six. Although easily excited, she was liked and spoiled by the other patients, who treated her quite as a child. The diagnosis was juvenile general paralysis. For three months before death she had stiffness and rigidity of the neck; she became drowsy and helpless, and there was an internal strabismus of the right eye. At the autopsy a generalised cerebro-spinal gummatous meningitis and universal peri-vascularitis and endarteritis were found; all the arteries of the circle of Willis showed a profound peri-arteritis and obliterative endarteritis; the peri-vascular and neoplastic infiltration was universal; it corresponded entirely in its histological characters with a gummatous meningo-encephalitis. At the upper part of the spinal cord the roots were

surrounded by an infiltrating exudation quite 3 mm. in thickness. The neoplastic formation consisted of proliferated, branched, and spindle-shaped connective-tissue cells, and round or oval cells forming all stages between lymphocytes and plasma-cells; there were also macrophages, but polymorphonuclears were conspicuous by their absence; large numbers of the cells were undergoing a granulo-aqueous degeneration. Considering the universal vascular change and peri-vascular infiltration affecting the vessels of the brain and spinal cord, including the roots, it was astonishing how little had been the destruction of nerve-cells and fibres.

Another case of *syphilis hereditaria tarda*, which occurred at Claybury, has been investigated by Dr. Rondoni.

The patient, a girl, was healthy until aged 14 years; she afterwards became dull and apathetic, suffered with fits (apoplectic), coarse tremor of arms, nystagmus, exaggeration of knee-jerks, and inequality of the pupils. The family history obtained was two miscarriages; one boy who lived only seven months; a boy who lived fifteen months; then the patient, who died at the age of twenty-three; then came a healthy living girl, and lastly a girl who lived only sixteen months. Rondoni found an old diffuse, endarteritis syphilitica with numerous small aneurysmal dilatations, especially of the arteries of the basal ganglia. The arteritis was evidently of long standing, for many of the small vessels in the basal ganglia showed calcareous infiltration and patches of old softening, which can be correlated with the apoplectic fits. The small veins are also affected. Rondoni considers this to be a case of *syphilis hereditaria tarda* of the nervous system similar to the cases of Homen and La Chapelle. The cases of Homen differ only because they were familial (five brothers and sisters). In Homen's cases there were diffuse degenerative changes in the cortical cells without granulation in the ependyma, arterial lesions and softenings in the basal ganglia, little proliferation of glia, and only a slight perivascular infiltration. Homen's cases were as follows: At the ages of twenty, twelve, and twenty, the disease manifested itself by phenomena of vertigo, headache, disturbances of general well-being, diminished intelligence and weakness of memory, diffuse vague pains in the legs, oscillating gait and difficulty of speech; the intellectual loss proceeded to an actual dementia; the speech disturbance was rather inability to initiate than to articulate. Spastic conditions in the legs came on, also in the arms; in both situations it progressed to actual contractures. Pupil phenomena and anæsthesia were absent. In all three sisters a certain degree of infantilism occurred.

In both the cases I have related the patients showed a marked degree of infantilism of the generative organs. In view of the results obtained by Kretschner, who has shown that *syphilis hereditaria tarda* is associated with a lymphocytosis of the cerebro-spinal fluid, it would have been interesting if lumbar puncture had been performed in these cases.

Cases have been recorded of syphilitic disease of the brain, the spinal cord, their cavities and vessels (Dowse, Siemerling, Bury, Böttiger, Pick, Hutchinson and others). The nervous disease of the child began in the case reported by Dowse at the age of ten, Siemerling's at the age of six, and Bury's at the age of eight. An especially large single gummatous tumour situated in the occipital lobe which had led to erosion of the cranium has been recorded by Hutchinson in a girl of sixteen. Hutchinson looked upon the case as one of *syphilis hereditaria tarda*.

As in acquired syphilis so in the congenital form, cases of so-called syphilitic meningitis or meningo-myelitis are in reality not localised to the spinal cord, but affect also the base of the brain and its stem; they are really cases of cerebro-spinal meningitis in which the cerebral symptoms are slight and the spinal symptoms obtrusive; consequently it is not surprising that there are no recorded cases, so far as I can find, of congenital spinal syphilis, although in all cases of diffuse meningitis and arteritis the spinal structures participate in the form of disease of arteries and veins, of circumscribed and diffuse infiltrating gummatous neoplasms, meningitis and neuritis affecting the anterior, and especially the posterior spinal roots. In fact all the evidence tends to prove that in congenital syphilitic disease of the nervous system, multiple combined affections are the rule, and it seems probable that tissues which are undergoing development afford a more congenial soil for the specific organism to grow and multiply in; consequently infection of the central nervous system is especially liable to lead to severe disturbances and loss of function and early death when it is not immediately fatal. Moreover, although other ætiological factors, *e. g.* alcoholism and mental stress, do not directly play a part, yet it is probable that alcoholism, and particularly a neuropathic or psychopathic taint in progenitors, play an important part as contributory factors in the later development of general paralysis, optic atrophy and tabes, also epilepsy, hysteria, and other neuroses of congenital syphilitic children.

SYPHILITIC ENCEPHALITIS.—A localised encephalitis, apart from gummatous meningitis and arteritis, is extremely rare. Little's disease and spastic hemiplegia have been attributed to an encephalitis of congenital syphilis, but Oppenheim and Casirer, in their valuable monograph on encephalitis,

express the opinion that syphilis plays an unimportant part in the production of encephalitis. Max Nonne, from his experience, comes to a similar conclusion, and Sachs, who has had a very large experience regarding encephalitic paralysis of children, only found two cases of hereditary syphilis in 200 cases of congenital paralysis. Moreover, the post-mortem experience of Von Recklinghausen is to the effect that a true encephalitis is rare in hereditary syphilis. He found encephalitis only twice in 45 cases of hereditary syphilis occurring in the post-mortem examination of 1600 children. Possibly, however, had a microscopic investigation been made as Ranke has done, the results might have been different. Fournier, Gilles de la Tourette, Charcot, Heubner, Franke and Erlenmeyer, on the contrary, consider congenital syphilis an important cause of Little's disease. My own experience would assign congenital syphilis a place inferior to asphyxial conditions at birth, head injury, and the infectious diseases of childhood; not that I disbelieve the important influence of congenital syphilis in its production of encephalitis, but its relative infrequency I would explain by the fact that if the living virus gains access to the cranio-spinal cavity, in the great majority of cases it proves fatal within a short time owing to spirillar septicæmia, as Ranke has shown; or the infant, if born alive, dies of hydrocephalus, meningitis, or convulsions within a short time after birth.

CONGENITAL SYPHILIS AND EPILEPSY.—Convulsions in early infancy are a common cause of death of infants the subjects of congenital syphilis; they may own many causes. Thus a child with syphilitic cachexia may die from convulsions brought on by improper feeding, teething or infectious disease, or it may die from convulsions due to meningitis syphilitica. It is almost impossible in an infant to decide what is the cause of the convulsions; a *post-mortem* examination with microscopic investigation could alone decide whether the convulsions were due to invasion of the central nervous system or not by the syphilitic organism.

The subjects of congenital syphilis may in later life develop typical idiopathic epilepsy; unless a careful inquiry be made into the family history it would be manifestly impossible to assert that an hereditary neuropathic taint was not the more important cause of the epilepsy than the congenital syphilis; still, there is reason to believe that acquired syphilis may be a direct cause in certain instances of the manifestations of epilepsy in later life, and Fournier went so far as to say that a man who became first affected with epilepsy after he had reached forty years of age owed the epilepsy to syphilis acquired a long time previously; therefore it

is possible that some cases of epilepsy are due to congenital syphilis. In fact I know of several cases in which congenital syphilis seems to be a reasonable explanation of the onset of epilepsy in adolescence; one in particular I have in mind. A young gentleman suffered with epilepsy first at the age of seventeen. I could find no cause in the family history, there was no evidence of epilepsy or of other neuroses or psychoses in the family. Examination of the eyes ophthalmoscopically of this apparently healthy, untainted young man showed a definite choroido-retinitis.

The figures (Figs. 4 and 5) exhibit two well-marked congenital syphilitics, the subjects of epilepsy and imbecility, and I am sure, from the study of pedigrees obtained from imbecile asylums, that congenital imbecility and epilepsy is not a very infrequent result of congenital syphilis. A great many of these cases, however, which are diagnosed epileptics the subjects of congenital syphilis, subsequently turn out to be juvenile general paralytics.

Localised softenings may act as a source of irritation, and give rise to epilepsy with or without paralytic phenomena. Thus an epileptic, feeble-minded woman, an inmate of Claybury Asylum, told me that she had been paralysed in her right side from her earliest infancy; examination of the eyes showed a well-marked choroido-retinitis indicative of congenital syphilis; she had, besides, evidence of old interstitial keratitis and squint; these two latter eye affections she suffered with in early life, and later on she developed epileptic fits. I have seen many cases of syphilitic brain disease in adult life followed by softening or gummatous meningitis near the motor area act as a source of irritation, at first causing unilateral Jacksonian epilepsy, but the convulsions after a time have become so generalised that they were indistinguishable from ordinary epilepsy. Such cases are not so uncommon in asylums. Those persons suffering with epilepsy due to organic brain disease often have unequal pupils and a certain amount of dementia, and therefore are sometimes diagnosed as general paralytics.

Congenital syphilis and symptomatic epilepsy are both fairly common diseases, consequently because patients show stigmata of congenital syphilis on the body or the blood gives the Wassermann reaction, it does not necessarily follow that there is a causal connection between the epilepsy and the syphilis, unless it can be proved that the syphilitic virus has so damaged the brain in the neighbourhood of the motor area that the lesion can act as a source of irritation. In many of the cases of congenital syphilis and epilepsy there is a family history of insanity or epilepsy either

in the direct ascendants or in the collaterals; the syphilis in such cases may therefore only be a co-efficient in the causation of the epilepsy or insanity. The following case may be attributed to congenital syphilis: A. B—, formerly an inmate at Darenth Asylum, was sent to Colney Hatch Asylum as a dangerous epileptic. He was scarcely able to speak, being able only to say a few simple words. He had a low forehead, prominent development of the lower part of his face, a saddle-shaped nose, notched peg-shaped teeth, and very marked linear scarring all round the mouth. He was stunted in growth, but the genital organs were well developed. He remained for some time in the same condition. The fits were epileptic in character, the pupils equal and reacted to light and accommodation; there was no coarse paralysis (*vide* Fig. 5).

Some types of congenital feeble-mindedness due to congenital syphilis are shown in the accompanying photographs.

The important question arises, Can parental syphilis modify the germinal plasm so as to influence the proper development of its most complex and, functionally as well as structurally, highly differentiated product—the cerebral cortex?

Fournier, Erlenmeyer, Heubner, Fischl and many others have cited some very remarkable instances of congenital syphilitic children apparently spontaneously developing epilepsy. The statistics at hand are not very valuable. According to Veit (Wuhlgarten) the proportion of congenital syphilitics among the epileptics was 7 per cent. Binswanger asserts that congenital syphilis plays a much more important predisposing rôle in the production of epilepsy than is generally imagined. He speaks of a dyscrasic form of congenital syphilitic epilepsy. I think it would be a legitimate conclusion to arrive at, that congenital syphilis was the cause of symptomatic epilepsy if the parents of the syphilitic child both came from sound stocks in which there was no previous epilepsy, migraine or insanity.

Without attempting to give any precise data I am of opinion that syphilis and alcoholism of the parents may influence the germ-plasm and *per se* lead to the production of imbecility and symptomatic epilepsy; but seeing how very common the combination of syphilis and alcoholism is, the fact of a child of parents so affected suffering with epilepsy may be only coincidence. If, as in the case of juvenile general paralysis and optic atrophy, syphilis were an invariable antecedent in epilepsy, or even if it were a frequent antecedent, it might be conceded that the syphilitic poison was epileptogenous; but inasmuch as epilepsy occurs very fre-

FIG. 1.



FIG. 2.



FIG. 5.



FIG. 3.



FIG. 4.



quently in communities where syphilis is unknown, and among total abstainers almost as frequently as in drinkers, the causal relationship of syphilis and alcoholism in the parents with epilepsy in the offspring is uncertain. What certainly is true is that if there be a neuropathic or psychopathic taint in the progenitors, alcohol and syphilis will singly or combined tend to bring out that neuropathic taint—and were it not for the fact that both these poisons are *deadly* as well as devitalising, the effects on humanity would be cumulative and lead to racial annihilation. Thus, after all, these two scourges of humanity may lead to the survival of the socially and morally fittest, by killing the progeny of those stocks which have an inherent lack of judgment and highest control, in this way counter-balancing to some extent the degeneracy which they produce and are directly responsible for. Venereal diseases of the parents are much the most potent factors in the production of sterility, miscarriages, abortions and infantile deaths, in this respect markedly contrasting with tuberculosis, in which there is neither sterility nor miscarriages and abortions. Chronic alcoholics are improvident and have numbers of children, but do not rear them; generally this is the result of careless and improper feeding. Venereal disease is so frequently associated with chronic alcoholism that the progeny of drunkards is greatly diminished in consequence of their much greater liability to contract these diseases. Consequently statistics relating to alcohol *per se* and its causation of miscarriages, still-births, and children dying in infancy, are open to this error, that syphilis may be co-operating.

SYMPTOMATOLOGY OF CONGENITAL SYPHILIS OF THE BRAIN.

The pathological changes in the central nervous system met with in congenital syphilis are similar in all respects to those found in adults due to acquired infection. Necessarily, therefore, the symptomatology is very similar.

(1) *Convulsions*.—I have already pointed out that infants and young children born of syphilitic parents very frequently die of convulsions. Barlow and Bury likewise point out the frequency of early convulsions in congenital syphilitic children; some of their cases exhibited this symptom quite early. Their experience is thus summed up: “The earliest case of convulsions with subsequent post-mortem verification of extensive meningeal changes was observed by one of us in a child, aged four months, but we have notes of several at the age of three months, without post-

mortem verification, and one of a syphilitic infant, who had ten or twelve fits daily from the age of fourteen days to seven months." There is practically no period after birth up to two years in which convulsions may not occur. The fits are usually bilateral, consisting of tonic and clonic spasms; in some there is opisthotonos, spasms with persistent retraction of head and neck, and laryngismus stridulus not infrequently occurs. These authorities remark that it is important to note that syphilitic infants simultaneously or shortly after the appearance of the rash and snuffles may develop bilateral fits and laryngismus; months or years may then elapse without fresh symptoms, as if the virus were latent, and then a unilateral spasm or paralysis may ensue. The following example is given: T. H—, snuffles at four weeks and probably pemphigus succeeded by bilateral fits, three or four a month up to one year. The child was unable to sit up till the age of three, and did not walk till four years of age. At the age of four it had two right-sided fits within six months followed by right hemiplegia and dysarthria. She was seen again at ten years of age and exhibited the usual well-marked stigmata of congenital syphilis. The right eye was blind and there was extensive detachment of the retina. The left showed atrophy of the disc and old choroiditis. There was some paresis of the right upper and lower limbs, but no spasm, and there was a slight arrest of development (as shown in length and circumference) in the right forearm as compared with the left. There was no evidence of paralysis of any cranial nerve. She heard and understood many things which were said to her, and answered some questions, but could not be trusted in her replies to questions in testing common sensation and special sense. There was a slight articulatory defect, as of a young child who had not long learned to talk. She was docile, but distinctly retarded in her intellectual development for a child nearly eleven. She died of nephritis, and at the post-mortem her brain showed remarkable sclerosis of both hemispheres, the left being more affected than the right, with marked shrinkage in both transverse and longitudinal measurement. There was also extensive endarteritis of all the arteries of the circle of Willis and their branches.

(2) *Headache and irritability*.—Headache, worse at night, is a sign of brain disease due to acquired syphilis, but according to Barlow and Bury it is also met with in brain disease due to congenital syphilis. Definite complaints of headache are not made by infants and young children, but these authorities state that their experience shows that syphilitic infants sleep badly; they have screaming fits, and they have known cases of torpor, paresis, and unilateral convulsions ushered in by excessive irritability

and stiffness of the neck, either with the head retracted or held to one side.

(3) *Hemiplegia and other motor signs.*—A frequent symptom of congenital syphilitic brain disease is hemiplegia; it is usually preceded by unilateral convulsions, and the convulsions may occur at intervals again on the paretic side. In some cases there is an onset like an apoplectic fit, and without any warning the child may fall down unconscious and remain so for a varying period of time. In other cases the child may be irritable, restless, and if old enough it may be noticed that it has suffered with headache and attacks of vomiting; suddenly, or perhaps comparatively suddenly, and without loss of consciousness, there may be a loss of power on one side of the body and the speech may become thick and indistinct. Attacks of drowsy torpor and somnolence, so characteristic of cerebral syphilis in the adult, may also occur in the child.

(4) *Affections of speech.*—Speech defects of the nature of dysarthria or aphasia frequently occur, but as a rule they are more temporary in cases of congenital syphilitic hemiplegia than when occurring in the adult; Barlow and Bury state that—"in many of the initial attacks of hemiplegia paresis of limbs, so far as its gross indications are concerned, clears up to a great extent, and the paresis of the face to a marked extent. The only vestige may be that the child does not use the arm and hand which have been affected quite as freely as those of the opposite limb." But as in the adult form, so in the congenital, there is a great proneness to subsequent attacks, after which a spastic condition may supervene; following an attack affecting one side of the body there is a marked liability to affection of the opposite side. In such cases an endarteritis may be suspected. In the hemiplegic condition of children, speech affections are, as a rule, much more transient than in hemiplegias of adults. Some interesting cases are recorded by the above-mentioned authors.

(5) *Affections of cranial nerves.*—Any one, or several of the cranial nerves, may be affected, apart from evidence of disease of the brain or definite meningitic symptoms; the nerve affection may be unilateral, or both sides may be affected, or several pairs of nerves; again, separate portions of the third and fifth nerves may be paralysed; occasionally, but rarely, the facial nerve is affected (*vide* case, p. 8).

Affections of the third and sixth nerves are not uncommon, giving rise to strabismus, and Hutchinson has recorded two cases of ophthalmoplegia externa in congenital syphilis. Nerve-deafness is not uncommon, and I have met with instances in the asylums: it is, however, rare as compared

with primary optic atrophy. The deafness comes on mostly between the periods of five years before and five years after puberty; it is bilateral, painless, and unattended by otorrhœa. In a number of the cases bone-conduction is absent. The following case, among others, may be cited: A young woman, aged 18 years, was admitted to Colney Hatch Asylum suffering with imbecility and impulsive conduct, amounting to a mild form of mania. She was absolutely deaf, but she was able to talk. She began to lose her hearing at eight, and in two or three years had become stone deaf. There were signs of old keratitis and notched teeth, but she was not undersized. She was soon discharged as recovered.

According to Gray, many authorities consider that congenital deaf-mutism is often due to inherited syphilis, and on this account the following case is of interest: A congenital deaf-mute was admitted to Claybury at the age of nineteen, and after being in the asylum for some time was discharged. He was, however, readmitted on account of suicidal impulses and mania: he died at the age of thirty-nine. The cerebro-spinal fluid gave the Wassermann reaction. The fourth ventricle was slightly granular, but the microscopic examination of the brain showed no signs of general paralysis. Very frequently the nerve-deafness of congenital syphilis is accompanied by interstitial keratitis, but the notes do not point to this condition, nor to any syphilitic stigmata on the body, so it is doubtful. Still, the positive Wassermann reaction and the granular ventricles suggest the existence of latent or active syphilis, and it will be interesting to know what morphological changes Mr. Sydney Scott finds in the internal ears. As he made special examination of the patient's ears during life the temporal bones were removed and forwarded to him. This case suggests the desirability of a systematic examination of deaf-mutes by the Wassermann test.

PARASYPHILITIC (METASYPHILITIC) AFFECTIONS OF THE NERVOUS SYSTEM DUE
TO CONGENITAL SYPHILIS.

The diseases which are generally recognised as such are general paralysis, tabo-paralysis, tabes dorsalis, and optic atrophy. These diseases are really a single morbid entity owning the same cause, insidious in onset, progressive in character, and uninfluenced as a rule by anti-syphilitic remedies. These various clinical types of parasyphilitic disease are the result of a primary neuronc dystrophy; they have a similar pathogenesis, and may occur simultaneously or successively in the same individual. Congenital syphilis may result in any of these forms of parasyphilis, but

general paralysis and optic atrophy are the most commonly met with. Undoubtedly some of the cases of optic atrophy are of a truly syphilitic nature and may be subsequently followed by parasyphilis in the form of general paralysis. General paralysis as the result of congenital syphilis is not, however, common, for the reasons before mentioned: it may begin at any age; the youngest I have known commenced at eight years, and death occurred at sixteen, the eldest occurring at twenty-eight years with death at thirty-one. In 500 post-mortem examinations made at Claybury Asylum on general paralytics, there were ten cases of the juvenile form, and of these five were males and five were females. The sexes were affected equally as might be expected. Professor Clouston in 1877 described a case of general paralysis in a boy, aged 16 years, and he pointed out that clinically and pathologically the disease that affected his patient in no way differed essentially from the adult form: he termed it developmental general paralysis, and it was looked upon by him as an extremely rare condition. Since then a great number of cases have been recorded, and important papers have been published on the subject by Régis, Alzheimer, and others. The disease formed the subject of a paper by myself on twenty-two cases in the 'Archives of Neurology,' vol. i, and a second paper by Dr. Watson in vol. ii, and I claimed that these juvenile cases, having been proved to occur in the great majority of instances in the subjects of congenital syphilis, supported the contention of Fournier that syphilis was essentially the *fons et origo* of general paralysis, for the other ætiological factors which had been claimed to cause general paralysis, viz. sexual excess, mental stress, injury, and particularly alcohol, can in the majority of these juvenile forms be eliminated. Moreover, I have shown that a psychopathic heredity as a rule plays little or no part in this acquired disease. Numbers of cases have occurred in the asylums since the publication of these investigations which have confirmed the results I then obtained; it will therefore be unnecessary to do more than summarise the principal facts concerning the parasyphilitic affections resulting from congenital syphilis, illustrating the same with a few typical cases. The majority of cases admitted to asylums, unless they present well-marked stigmata of congenital syphilis, are diagnosed as imbeciles or epileptic imbeciles, yet careful inquiry from the parents of a considerable number, shows that until puberty these children were up to the average standard in intelligence, for they usually attained the sixth standard in the board schools; others, however, were feeble-minded and backward from birth; as a rule the signs of active degeneration commenced about the time

of puberty. It is not uncommon to find children admitted to the schools for the blind with optic atrophy coming on before puberty in early or later childhood. Some of these cases are feeble-minded, and some are intelligent and capable of training. At puberty or early adolescence various signs of cerebral decay, *e. g.* changes in the habits and disposition, inability to learn, weakness of memory, etc., may be noticed, or the patient may have a fit, followed by other fits. Sooner or later the signs of mental disorder are sufficiently pronounced to necessitate the removal of the patient to an asylum. Thus two brothers, sons of a dissolute father, were admitted to one of the London County Asylums; both had become blind before puberty and at about the same age. The mother had had miscarriages, followed by the birth of these two boys; they were good-looking and presented no obvious signs of congenital syphilis, and they were intellectually capable boys before they commenced to have fits (*vide* fig. 2). They were sent to the asylum as epileptic imbeciles, and died there some years after admission.

These cases of optic atrophy associated with juvenile general paralysis are frequently accompanied by changes in the spinal cord of a tabetic character. Ataxy of the limbs in these congenital cases is not common. I have met with three definite cases, one in which there was a spontaneous fracture of the femur and two other cases. Perhaps the most interesting of these two was that of a young man, aged 18 years, in whom the disease terminated fatally within four months of the onset of pronounced symptoms. The history obtained from the mother was briefly as follows: Her husband drank, but always remained in employment. She had had three children, all alive and healthy, then two were born dead; the sixth died at seven months and the seventh is the patient. The husband was not a steady man and went with other women. There was no insanity or fits in the family on either side. The patient, she said, was a bright, intelligent lad, although weakly and delicate. He was an excellent musician and was always sober and steady. For some time he had complained of pains in his legs and a feeling as if they were giving way under him. Then he had the delusion that someone was coming to rob the house and kill his mother. His speech became affected, and he was removed to University College Hospital and subsequently transferred to Colney Hatch Asylum. On admission I noted that the pupils were small and reacted slightly to accommodation but not to light. The speech was tremulous; there was elision of syllables and slurring of words. There was tremor in his writing and a marked tremor of the tongue and lips. There was slight rotatory

nystagmus but no squint. The fundi were normal, and there was no concentric limitation of the field of vision. He stood with a wide base and swayed a good deal on closing the eyes. The knee-jerks were absent, but the muscles responded to faradism. There were linear cicatrices at the angles of the mouth; the teeth were decayed and the incisors were cupulated and peg-shaped. He had a semi-imbecile paretic expression of foolish contentment and his conversation was incoherent, but he exhibited no delusions while in the asylum. He became progressively more paretic and demented, and died within four months of the onset of symptoms. This is the most rapid case I have seen; probably excessive masturbation, which he practised after the mental symptoms developed, hastened the progress of the mental decay. At the post-mortem the typical lesions of general paralysis were found in the brain, together with a naked-eye sclerosis of the posterior columns. The liver showed pericapsular, perivascular, and pericellular fibrosis, characteristics of congenital syphilis.

A considerable number of cases of juvenile general paralysis are sent to the imbecile asylums of the Metropolitan Asylums Board, and if they are troublesome, necessitating more care and attention than can be given, they are transferred to the London County Asylums—*e.g.* D. McD—, aged 18 years, was admitted, October 28th, 1907, to Bexley Asylum, having been transferred from Tooting Bec, where he had been sent certified as an imbecile. He is said, however, to have reached the seventh standard in the board school when aged fourteen, and up to sixteen was able to earn his living. There is a history of a fall from a ladder, injuring his head when he was aged twelve. The notes state that he was undersized and that he had carious, syphilitic teeth, the genital organs were undeveloped, and he was only 4 ft. 9½ in. in stature. There was a slight ptosis of the left eye; the pupils were unequal, outline irregular, the left larger than the right, with both inactive to light. The knee-jerks were present. There was no control of the sphincters. His mental state was thus described: The attention is obtained with difficulty, and he is unable to comprehend what is said to him. He has little or no knowledge of his surroundings, and calls everybody “father” or “mate.” He is too demented to test his orientation of time and place; there is no evidence of hallucinations or delusions. He is noisy, restless, resistive, and destructive. His speech is markedly tremulous. No history of syphilis was obtainable, but I ascertained that the father died in Guy’s Hospital, and information obtained from the registrar points to the fact that he had syphilis; moreover, a brother of the patient has been admitted to the asylum suffering with

general paralysis, aged twenty-nine. The notes state that he has had acquired syphilis. The patient died after a residence of six months of double lobar pneumonia. The post-mortem examination showed the following changes in the brain:

The brain was forwarded to the Pathological Laboratory for examination: Weight, 1175 grm.; right hemisphere, 510 grm.; left hemisphere, 478 grm.; pons, etc., 187 grm. All the convolutions are small, not much wasting, no local wasting. Adhesions along middle line of the two hemispheres in front. Convolutional pattern complex. Calcarine fissure in left hemisphere comes a long way round on the external surface. Calcarine in right hemisphere ends in the vertical fissure of Seitz at the pole. There is comparative to the right hemisphere, an obvious failure in development of the parietal lobe in the left hemisphere. The Sylvian fissure is horizontal in both hemispheres. Lateral and fourth ventricles granular. Spinal cord shows apparent degeneration in posterior columns, and the grey matter looks more vascular than normal, and the cord generally is smaller than natural. There is nothing further noteworthy in the post-mortem notes except that death occurred from double lobar pneumonia (red hepatisation in both lungs) of about four or five days' duration.

The microscopic examination of the brain and cord exhibited the following points of interest: The cortex of Broca's convolution showed more pronounced changes than the top of the ascending frontal convolution, but in both situations the same changes were observed. There was increased vascularity; many of the vessels showed an infiltration of their lymphatic sheaths with lymphocytes and plasma-cells. The endothelial cells lining the vessels and forming the walls of the capillaries were swollen; the nuclei, instead of staining deeply, were swollen and pale in coloration. Rod-cells were met with occasionally in sections of Broca's convolution; also a few sprouting capillaries were to be found. The neuroglia cells were not found in any numbers in the grey matter of the cortex, but they were very numerous in the white matter. There was some sub-pial felting of glia, and the leptomeninges in places exhibited a lymphocyte and plasma-cell infiltration. The vascular and glia changes were not, however, marked. The cells were well shaped in the majority of instances, and there was no marked distortion of Meynert's columns in the ascending frontal convolution; the cell changes were more pronounced in Broca's convolution. The cells showed a large clear nucleus; the processes in many instances appeared broken off or absent, and many of the cells were crumbling at the borders. Occasionally two nuclei or a nucleus dividing could be seen

in the ganglion-cells. All the cells examined by the Nissl method showed a diffuse uniform purple staining, with absence of Nissl granules—an appearance that is consistent with prolonged high fever. The notes do not say so, but it is probable that during the last twenty-four hours of life, when he lay in a comatose condition, he had hyperpyrexia. All the central nervous system, including the spinal cord, showed this change in the ganglion-cells. The spinal cord showed very marked changes, the leptomeninges and the vessels showed infiltration with lymphocytes and plasma-cells; there was well-marked sub-pial felting indicative of chronic change. There was glia-cell proliferation most marked in the posterior columns and around the central canal, which was obliterated and filled up by proliferation of the cells of the ependyma and neuroglia. By the silver Cajal method the cells showed the fibril structure in the majority of instances fairly well, especially in the deeper structures of the grey matter of the cortex. The small and medium-sized pyramidal cells were considerably diminished in numbers; also the cells of the deep polymorphic layer. The molecular layer was almost absent and replaced by glia tissue.

The microscopic appearances suggest that this lad was a feeble-minded boy in whom the brain had participated in the general bodily deficiency; the pattern was fairly good and very complex, but all the convolutions, especially of the parieto-occipital and frontal regions, were very small—almost a *microgyria*. There was a progressive dementia in this case, but there was also a condition of amentia or arrest of development proportional to the general bodily arrest of development, and possibly associated particularly with the infantile reproductive organs. He never had fits, or hallucinations or delusions; probably this may be associated with the fact that there was comparatively little vascular and glia change. The whole nervous system, including the spinal cord, was affected. The changes in the nerve-cells were partly due to arrest of development and partly to a progressive primary decay, together with a universal affection of the cells of the whole nervous system of a bio-chemical nature, as revealed by uniform dull purple staining with absence of Nissl granules, due to the effects of toxæmia and hyperpyrexia, and not related, therefore, to the mental symptoms that characterised the disease.

Juvenile general paralytics diagnosed as epileptics.—Some of the cases of juvenile general paralysis are sent from epileptic colonies or Dr. Barnardo's Homes. The following case of a feeble-minded boy who was sent to Barnardo's Home is also of interest, because the first sign of the disease was manifested at the age of eight, when he had a fit. F. J— at

the age of nine, was brought to Charing Cross Hospital suffering with epiphysitis. He had typical Hutchinsonian teeth, rhagades all round the mouth, choroido-retinitis, internal strabismus of the left eye. Under mercurial treatment the epiphysitis healed completely. The mother stated that prior to his birth she had had several miscarriages and two still-born children. She herself has, however, never suffered in any way. The next child is a girl; she presented no symptoms of syphilis, except internal strabismus of the left eye. After attending nearly a year, his mother came and thus described several fits which he had had at school. He went to school all right, but while there he passed a motion unconsciously. He was brought home, cleansed, and returned to school, "more to get him out of the way than for what he learnt;" he was quite an infant in mind. At eleven o'clock he was again brought home in a fit; he was quite unconscious, there were no clonic spasms, but he remained unconscious for one hour. The teeth were clenched, but he did not bite his tongue. The mother said that two years previously he had had a similar fit. On another occasion he was observed by the master to act strangely, for he kept rubbing out and writing the same word automatically. He was quite unconscious of what he had been doing. Later he was sent to Dr. Barnardo's Home, and I lost sight of him for four or five years until he was admitted to Colney Hatch Asylum. His appearance was but little changed: he looked about ten years of age although he was fifteen. The tongue was tremulous and jerky, likewise there was a well-marked tremor of the lips; the speech was muttering, hesitant, tremulous and incoherent. He seemed to understand only partially what was said to him, and although he did not recognise me, he knew his mother. The knee-jerks were absent on both sides; the pupils were unequal, dilated, and irregular, reacting sluggishly on convergence, but not to light. He did not respond to the calls of nature. There was no hair on the pubes, and the genital organs were quite infantile. The dementia and paresis progressed rapidly, but he manifested no evidence of delusions or hallucinations. Death occurred two months after admission from exhaustion. The brain, macroscopically and microscopically examined, presented all the characters of general paralysis; the arteries showed no syphilitic affection, therefore the fits at the age of eight were not due to a true syphilitic brain disease, but were the first sign of paralytic dementia. There was a scar of an old gumma on the liver, and both this organ and the kidneys showed the characteristic changes of congenital syphilis. The testicles showed no spermatozoa.

General paralysis in parents and offspring.—In about 20 per cent. of the cases of juvenile general paralysis I have found that the father has died in an asylum of general paralysis; seeing that there are a large number of female paralytics (the proportion in the asylums being three males to one female), it is rather remarkable that in sixty cases of juvenile general paralysis I have not met with an instance in which the mother has died of general paralysis. In the statistics of relatives which I have been engaged in collecting, and which are dealt with fully in the Huxley Lecture (Appendix), it has been shown that relatively few cases of parents and offspring occur in which general paralysis is the disease affecting either or both. Yet we see that similarity of the mental disease occurs in 20 per cent. of the instances, and according to my experience the father is the parent invariably affected. In other forms of insanity due to the neuropathic taint the mother transmits twice as frequently as the father, and daughters are affected twice as frequently as sons. The difference is this—that general paralysis is an acquired disease due to the late effects of the syphilitic virus, and hereditary neuropathic tendency plays little or no part in the production of this organic brain disease. Now while I do not say that instances may not occur of the mother suffering with general paralysis, and one or more offspring dying later of the same disease, I am of the opinion that as I have not met with them they must be very rare indeed. How can this extreme rarity be accounted for? Clearly neuropathic tendency cannot play an all-important part, otherwise we should expect to have had instances of female paralytics with paralytic offspring; juvenile paralysis occurs with equal frequency in the two sexes as might be expected, seeing that there is a comparative numerical balance of the sexes, and the essential cause is syphilis; unlike the conditions met with in the adult form, the syphilitic virus is liable to affect both sexes equally. The fact that women acquire syphilis much less frequently than men would not account for the fact that I have found no instances of mothers with general paralysis having paralytic offspring. How can the fact be accounted for? Most of the mothers of paralytic offspring have not apparently suffered with any severe symptoms; they have been immunised. Again, a large number of the paralytic women in asylums have undoubtedly been prostitutes, and have therefore become sterile; in connection with this it may be mentioned that 50 per cent. of the female paralytics dying at Claybury Asylum were found, post-mortem, to have suffered with old salpingitis. Moreover, a woman who had been infected and afterwards suffered with general paralysis is less liable to have living offspring.

Congenital syphilis and general paralysis in later life.—In my Croonian Lectures upon the “Degeneration of the Neurone” (1900), I remarked that it is very probable that some of the cases occurring in adults, in which acquired syphilis can be excluded with certainty, may still owe the disease to congenital syphilis. It is not even necessary, as quite one half of the cases show, that they should exhibit any external signs of congenital syphilis, for many juvenile cases can be proved beyond doubt, as the following cases I have collected show, to have been born of syphilitic parents; although manifesting themselves no external signs of syphilis, yet the history of miscarriages, still-births, and children dying in infancy of meningitis, hydrocephalus, or of brothers and sisters with well-marked stigmata or evidence of *syphilis hereditaria tarda*, disclosed the necessary proof of the congenital taint. Sometimes no history may be obtainable and there may be no signs of syphilis on the body; even in some of these cases a definite proof of the possibility of congenital syphilis may be forthcoming by a little investigation. Thus I was asked to see a case at Cane Hill Asylum, who was suffering from advanced general paralysis. He was almost speechless, had great difficulty of swallowing, his saliva dribbled from the angles of the mouth, all four limbs were in a condition of spastic contracture, and there was loss of control of the sphincters. There were no signs of syphilis on the body, and the only information obtainable was that he had had a fit at the age of eighteen, he had married when young, and his wife had given birth to a dead child, and had left him because of his “strange” conduct. He had more fits, and became slowly and insidiously more demented, and died at the age of twenty-eight. At the autopsy the most advanced condition of paralytic brain degeneration was found. I subsequently found that his father had died eight years previously of general paralysis in Claybury Asylum. I have once or twice met with instances of father and son being in the asylum together suffering with general paralysis. The case above referred to was one of juvenile general paralysis, commencing in adolescence, but running a slow course. Doubtless the fit at eighteen was the commencement of the brain decay, and had lumbar puncture been performed and the cerebro-spinal fluid been examined, a lymphocytosis and probably a positive Wassermann reaction would have been obtained. Just as in the cases of acquired syphilis the onset of general paralysis may in rare cases be greatly delayed, so in the juvenile form there may be great delay in the onset of the parasymphilitic affection. Thus a case of general paralysis died at Banstead Asylum which had previously been under Dr. Percy Smith at Bethlehem Hospital. This

woman had characteristic signs of congenital syphilis, but she did not manifest symptoms of paralytic dementia until she was thirty. She was an unmarried woman, and there was no evidence to show that she could have acquired the disease. Recently Christian Muller has put forward the same hypothesis to explain parasyphilitic disease affecting patients in whom no history of acquired syphilis can be obtained. He described two cases of women (virgins) who were the subjects of well-marked signs of congenital syphilis, and who died of general paralysis at the ages of forty-two and forty-three years. The symptoms were not noticeable until a year or two before death.

Tabo-paralysis and optic atrophy.—The following case of tabo-paralysis is of interest, as gastric crises at the age of nine were the first symptoms that brought the patient under observation.

P. C—, aged 9 years, was admitted to Charing Cross Hospital suffering with attacks of vomiting and occasionally diarrhœa. She had well-marked obtrusive stigmata of congenital syphilis, in the form of Hutchinsonian teeth and rhagades. I ascertained that the father had died some years previously at Banstead Asylum of general paralysis; his notes gave no history or signs of syphilis, although the fact of his having had syphilis was clearly demonstrated in his offspring—a not unusual occurrence. The mother had not suffered with any sign or symptoms, but prior to the birth of the patient she had had one miscarriage and two children born dead. The paroxysmal attacks of vomiting had commenced at seven years of age. She had become progressively enfeebled mentally, and was sent to Darenth, where I again saw her. She still suffered with vomiting and lightning pains; the pupils were unequal, inactive to light and accommodation; the knee-jerks were absent. Both eyes showed well-marked choroido-retinitis and optic atrophy. There was anæsthesia of the chest to light tactile impressions from the third to the sixth rib inclusive. Beyond childish mental enfeeblement there was nothing in her mental condition. There were no delusions, illusions, or hallucinations. Later she suffered with a sudden painless swelling of one knee, and a dorsal dislocation of the head of the right femur. There were no teeth in the lower jaw, and the alveolus was so much absorbed as to resemble the jaw of an old woman. Then she began to have fits and lapses of unconsciousness, sometimes biting her tongue and passing her urine and fæces under her. She died after some years' residence in the asylum of tabo-paralysis, the brain and spinal cord presenting the usual appearances met with in that condition.

According to my experience optic atrophy in juvenile general paralysis is commoner than in the adult form. A certain proportion of these cases are probably not true optic atrophy, but are the result of syphilitic brain disease.

Congenital syphilis and amentia terminating later in paralytic dementia.—As already remarked, in a large proportion (quite 50 per cent.) the syphilitic virus has led to a congenital amentia or feeble-mindedness from birth; this is shown by an absence of a large number of cells in the cerebral cortex as compared with the normal; by an imperfect development of the convolutions of the hemispheres, microgyria, and a comparative deficiency of weight of the cerebrum as compared with the weight of the cerebellum, pons and medulla, a deficiency which cannot be accounted for by the loss of substance due to the more acute degenerative process which has led to the superadded paresis and dementia. The mental symptoms in such cases are two-fold: those due to the arrest of development, viz. (1) imbecility or feeble-mindedness of varying grades, and (2) decay due to the primary decay and death of the neurones associated with acute destructive changes the result of congestive stasis and auto-intoxications.

Symptomatology of juvenile general paralysis.—I have shown that there is hardly any age at which para-syphilitic affections may not come on as a result of congenital syphilis, but the majority of cases show symptoms just about puberty; a fit occurs as the first warning, and the child is thought to be an epileptic. The child's character changes: if it is already feeble-minded it becomes more mentally deficient, that is to say, it begins to lose the little mind it possessed in its totality; if the child has shown itself possessed of a fair intelligence, the first signs of the disease may be a strange and unusual behaviour followed by a progressive loss of mind in its affective, cognitive, and conative aspects. The mother will tell you that her child, for no reason she knows of, is becoming childish and silly, sometimes bad-tempered and morose, whereas previously it was good-tempered, happy, and cheerful; while formerly careful and tidy in habit, it had become forgetful, careless, and untidy, given to doing strange things, showing less affection for the parents, giving up occupation for no apparent reason, and sometimes wandering from home. This *pre-paralytic stage* is often overlooked, but as the change of character and the dementia become more pronounced the facial expression alters either to one of depressive apathy or to one of foolish contentment, so that there is no art to find the mind's complexion in the face. Tremors of the face and tongue

with characteristic affections of the speech and hand-writing, as a rule, now become manifest, differing in no way from that of the adult form, the result of acquired syphilis. Since the more youthful patients are, as a rule, not anti-social, for they seldom have grandiose delusions or delusions of persecution, it may not be until they have had many serious convulsive seizures, become wet and dirty in their habits and obviously demented, that the parents of the lower classes consult a doctor; then a history such as I have given is frequently elicited from the parents. The constant symptoms in juvenile general paralysis are progressive dementia and paresis; grandiose delusions are rarely met with. When the disease does not become pronounced until some years after puberty there is often a history of masturbation, but, although this undoubtedly aggravates the course of the disease, it has not necessarily a causal relationship, but is rather an effect of the dementia.

Delusions of a sexual nature and grandiose delusions of wealth, strength and power coloured by the events of the period may occur just as in the adult form, but only according to my experience when the disease commences after puberty, the reason being that ambition for wealth and power and the sexual passion do not become an habitual incitation to conduct until some time after puberty; consequently, if the mental decay has set in before that period, these cannot become a revivable content of consciousness. The following case which I have recently seen illustrates this. A young woman, aged 21 years, the subject of well-marked stigmata of congenital syphilis, who commenced to suffer with fits two years previously, was admitted to Long Grove Asylum. The notes on her mental condition are as follows: She is restless, very talkative and expansive; she is going to give me medals, a carriage and four horses; everything in connection with her is fine and beautiful; the feeling of *bien être* is marked with an irresponsible sense of altruism. She is fairly orientated in time and place, though not knowing where she now is; amnesia is not noticeable.

After puberty consciously and subconsciously these desires are in one form or another always forming a part of the content of consciousness; there may be no outward manifestation thereof, for social amenities compel the normal individual to control, repress, and silence the inmost thoughts which nevertheless in their nakedness and crudity form the chief content of consciousness, or are ever on its threshold. But the neural structures, which are the last to be developed, are the first to go (Hughlings Jackson), and as the higher controlling centres decay and the auto-critical sense is

lost, then by the slightest suggestion, or even apparently without it, what is left of the psychic content bubbles forth, and what is left will be that which has by constant repetition become most fixed; now grossly exaggerated and coloured by associations, they come to resemble the fantastic fabrications which characterise many dreams.

Diagnosis.—There may be some difficulty in differentiating a case of juvenile general paralysis from dementia præcox, especially if there are no stigmata of congenital syphilis to warn one of the possibility of this rare disease. The characteristic signs and symptoms of paralytic dementia may be absent in the early stages, and in the absence of signs of congenital syphilis the case may be thought to be one of hysteria, epilepsy with imbecility, dementia præcox, or disseminated sclerosis. The hebephrenic or maniacal form of dementia præcox owing to the fact that it occurs in adolescence may be confounded with juvenile general paralysis. Of course it is possible for dementia præcox to occur in a congenital syphilitic, but if there are obvious stigmata one's suspicions would naturally be aroused that the case might eventually turn out to be paralytic dementia. The mental state of dementia præcox is, however, different to that of general paralysis; in the former it is the affective side of the mind which especially suffers and leads to strange conduct; the cognitive side of the mind, as shown by the patient's memory and intelligence, is relatively much less affected. In general paralysis, on the contrary, it is the cognitive side of the mind that is especially damaged, while the affective side, as shown by the emotional reactions of the physiognomy, is less affected. Whereas in general paralysis, on the one hand, the countenance often changes from one of depression to one of radial joy and exaltation; in dementia præcox, on the other hand, there may be no emotional reaction and the countenance retains a continuous stolid indifference. As a rule in dementia præcox there are auditory hallucinations, which are not usually present in paralytic dementia. Certain cases of general paralysis may have a mask-like expression of emotional indifference indicating that the affective side of the mind is profoundly affected, and therefore it is necessary for a correct diagnosis to look for the characteristic physical signs of general paralysis, which are seldom if ever wanting, and if there is still any doubt, lumbar puncture and examination of the cerebro-spinal fluid can be made.

Hysteria, hystero-epilepsy, and epilepsy.—Again, not a few cases in females may be regarded as hysterical in the pre-paralytic stage, or if there be fits, as epilepsy or hystero-epilepsy. The existence of dementia accompanied by pupil phenomena will lead to suspicions which can in most

cases be verified or negatived by lumbar puncture and examination of the cerebro-spinal fluid.

Disseminated sclerosis.—Some cases of juvenile paralysis have been diagnosed as disseminated sclerosis, but the intentional tremor of disseminated sclerosis is coarser and affects the large muscles of the limbs; the speech is affected, but it is scanning rather than hesitant, syllabic, and tremulous. There is frequently Babinski sign, which is very rare in paralytic dementia, likewise ankle clonus. The *bien être* expression, or *air de beatitude* of Charcot, gives a superficial facial resemblance to the expression of foolish contentment of paralytic dementia, especially when, as often happens, there is a mental enfeeblement. But the dementia is never so marked nor is it so steadily progressive in disseminated sclerosis; there is not a progressive paresis, but the remissions and attacks point to coarse foci of disease.

Neurasthenia cerebri.—Characterised by headache, loss of memory, weariness on mental or bodily exertion, loss of will-power, indecision of character in a young person the subject of congenital syphilis, may well make one think of the neurasthenic pre-paralytic stage of general paralysis. When there is a doubt about the diagnosis, examination of the blood and cerebro-spinal fluid by the Wassermann reaction and the latter for lymphocytes will help to clear up the diagnosis.

Duration and course.—I have seen cases which, like the adult form, may be galloping in their course—one terminated in four months from the onset (*vide p. 37*); as a rule, however, the disease runs a longer and slower course than in the adult; thus it proceeds to a more complete dementia and paralysis. The patient in the terminal stage is absolutely indifferent to his surroundings, speechless, and even swallowing with difficulty the minced food with which he has to be fed; there is marked wasting and contracture of the limbs, he passes his urine and fæces under him, and dies eventually either from broncho-pneumonia, tuberculosis, septicæmia, which may result from bed-sores, or suppurative nephritis, secondary to cystitis, and if not dying from one of these secondary or terminal microbial infections, he eventually and gradually succumbs to marasmus and asthenia.

Prognosis in disease of the nervous system due to congenital syphilis.—As in adult diseases of the nervous system due to acquired syphilis, so in the congenital form prompt, active anti-syphilitic treatment may be attended with remarkably favourable results. The first point, however, to attend to before giving a prognosis in nervous disease arising in

later childhood or early adolescence in a subject of congenital syphilis, is to determine whether the symptoms indicate syphilis or para-syphilis of the nervous system or are merely coincident ; this can be done by attention to the symptoms, their mode of onset and progress, and their response to anti-syphilitic treatment. Moreover, the greatest help can be obtained by the examination of the blood and cerebro-spinal fluid by microscopic and biochemical methods. A cerebro-spinal fluid that gives a Wassermann reaction points generally, though not necessarily, to parasyphilis. Parasyphilitic affections are invariably progressive ; when the brain is affected they are usually fatal within four or five years of the onset of definite symptoms of dementia and paresis, and they are uninfluenced by treatment. In other parasyphilitic affections, for example, optic atrophy and tabes, the prognosis, although not so bad as regards duration of life, yet offer an outlook most unfavourable, for many of the cases end in dementia paralytica and others terminate eventually in complete helplessness from blindness, imbecility, or other causes. In cases of epilepsy and feeble-mindedness the result of congenital syphilis, the prognosis is always bad, for the possibility of improvement of the mind or arrest of the fits is remote ; moreover, there is the probability that the case may terminate at puberty or adolescence in dementia paralytica.

In the case of nerve-deafness it is seldom that treatment does any good and the patient will become stone deaf. If, however, the child has learnt to speak and read for some years, as is usually the case, then, in spite of the deafness, it retains its speech faculties.

In cases of vascular and meningeal syphilitic inflammatory conditions the prognosis is more hopeful than in parasyphilitic affections, for they improve remarkably under treatment, but post-mortem investigation shows again and again the existence of widespread morbid processes which have left their scars if they are not even still active or capable of reactivation. If the disease can be treated in the early irritative stage, when convulsions occur and paralyses have not yet taken place, the prognosis is much more hopeful, for there can be no question that mercury and iodide, energetically but judiciously administered, will stay further progress and lead to a disappearance of symptoms. When, however, there is hemiplegia, it means destruction by softening occasioned by thrombotic sclerosis of vessels, and not only is the chance of relief by treatment less, but the probability of other vessels being similarly affected much greater.

Psychical symptoms, whether mania and motor restlessness or somnolence and drowsy stupor, are of grave omen, for the tendency is to dementia

Many cases of affection of the nervous system arising later in life might never have occurred if the congenitally syphilitic infants had been treated judiciously with mercury for a year or two instead of a month or two. Again, I have found in my experience how many cases of congenital syphilis which have developed such symptoms as keratitis, and nerve-deafness in later life have not been adequately treated. Mercury should be given in all cases of *syphilis hereditaria tarda*, and continued with periodic remissions for several years. An examination of the blood by the Wassermann method and if necessary an examination of the cerebro-spinal fluid should be made periodically. A negative reaction of the serum may lead one to remit the treatment, and according to my experience, if the blood-serum gives a negative result the cerebro-spinal fluid will also be negative and therefore lumbar puncture is not necessary. Should, however, the blood-serum give a positive reaction, examination of the cerebro-spinal fluid will afford very valuable information; a positive reaction points to a parasyphilitic affection, especially general paralysis. In juvenile parasyphilitic affections I have seldom seen any benefit derived from anti-syphilitic treatment; it may be given a trial in some selected cases, but disappointment at the result must not be felt if it is without benefit. There is little more to be done for parasyphilitic affections due to congenital syphilis than for the similar affections in adults.

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Microscopic Investigation of a Case of Tabo-Paralysis with Ophthalmoplegia Bilateralis.

By PIETRO RONDONI, M.D. Florence.

(From the Pathological Laboratory of the London County Asylums, Claybury.)

THROUGH the kindness of Dr. Mott I have had the opportunity of undertaking the histological examination of the following case of tabo-paralysis, which presents some interesting features, especially as regards the correlation of the anatomical changes with the clinical symptoms, the details of which were obtained from the London County Asylum at Long Grove, where the patient was an inmate. The following are the most important points regarding the clinical history of the patient kindly furnished by Dr. Bond :

J. R—, admitted May 22nd, 1908, aged 37 years, married. Occupation, cricket-ball maker.

Condition on admission.—The patient is described as a man of poor general bodily condition. Temperature, 97·4° F. Old scars on shin and abdomen ; small scar on wrist. Skin sallow, slight icteric tinge. Expression of face dull and confused ; marked transverse furrows on forehead ; eyebrows raised ; lack of tonicity of the other facial muscles, but no paresis.

Marked external strabismus, neither eye can be moved towards the middle line, and only slightly upward.

Marked ptosis, more on left side than on right. There is, therefore, paralysis or paresis of both internal and superior recti, inferior obliques and levatores palpebrarum. In respect to the last-named muscles, the one on the left side is more affected than that on the right.

There is complete paralysis of the sphincter of the pupils, which react neither to light nor to accommodation.

The pupils, though not reacting, are regular and equal ; size, 4·5 mm. The sight of the right eye is moderately good, but the left is very defective. The hearing is not impaired, and his articulation of words is normal.

There is no obvious inco-ordination of the limbs and the gait is normal; Romberg's sign is not present. There is no tremor; the knee-jerks are sometimes not obtainable; sometimes they are present, but are obtained with difficulty; there is no ankle clonus. The superficial reflexes are normal. There is a zone of light tactile anæsthesia involving the lower part of the chest and extending completely round the body; also a true girdle-anæsthesia. There seems also to be some general analgesia.

The patient cannot distinguish between the point and the head of a pin, denying that either gives him any pain. There is a moderate degree of anæmia, and there is some thickening of the radial artery. The heart is apparently normal, as are also the digestive and respiratory systems. There is a small scar on the inner surface of the prepuce; there is no enlargement of the inguinal or other lymphatic glands.

Mental state.—The patient generally lies quietly in bed, but unless watched he will occasionally get out and wander aimlessly about. On the day following admission, while lying in bed on the veranda, he suddenly attempted to escape in his night-shirt. He willingly enters into conversation; there is no defect of immediate comprehension, and his answers to questions are prompt and relevant. He is able to read and write, and performs mental arithmetic with average rapidity and accuracy. He is able to carry on an intelligent and coherent conversation, fully describing his work as a cricket-ball maker. Orientation in time and space are defective; he names the month and the year correctly, but says he has been here four months, and that it is Lambeth Workhouse. His statements vary from time to time, and he has no accurate memory of recent events. The gaps are filled with confabulations which are extremely susceptible to suggestion. By suggesting a few points to him, it is possible to induce him to relate a fabulous pseudo-history of yesterday's doing of any kind desired. The ideas mentioned in the certificate concerning the brother's imaginary defalcations are probably of this nature. It is significant that he now adds that he was successful in his summons at the courts for the return of his money, all of which is imaginary. Otherwise there are no delusions or hallucinations. The affective state seems to be one of placidity, and he professes to be perfectly contented. Apart from the restless wandering mentioned above he gives no trouble. He is clean in his habits, but does not attempt to occupy himself in any way.

Previous history (chiefly from wife).—Nothing unusual in childhood; suffered with chorea in boyhood. He is a steady and temperate man. He was infected with syphilis ten years previously. He was married in 1901,

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and has one healthy child. In 1894 he was in St. Thomas's Hospital for an operation on the nose (previous to the syphilitic infection). In 1905 he was in some hospital because "his sight became queer," and he remained an out-patient till July, 1907. He suffered also for some time from diarrhœa and tenesmus. From 1907 "his eyes seem to turn": he accused his brother of stealing things from him which he never possessed. He would "go off in a swoon" lasting half-an-hour, and said his inside felt "as if on fire." The doctor said he was suffering from vertigo and diplopia. He became rather better after three months but was bad again at Christmas. His family history is not known to his wife.

Progress of case.—The patient became more dull and confused. The knee-jerks disappeared completely. Sometimes he showed a liability to impulsive and foolish actions: he was very restless and often fell and bruised himself. In October a slight thickening of articulation was noticed. On October 28th a partial dislocation of the knee-joint occurred; and on November 9th a fracture of the femur, about six inches above the knee-joint, was recognised; but it was not possible to ascertain how this injury was produced, and whether a fall had occurred.

The patient became weaker daily, and bed-sores developed over the sacrum; finally he became comatose and died on November 15th.

Summary of autopsy.—There is commencing gangrene of the skin of the sacral region. Fracture of the lower portion of the left femur; the two fragments of the femur are atrophied and rarefied. The knee-joint is full, of a blood-stained fluid, with a quantity of fibrinous material. The lungs and the bronchi contain a considerable quantity of muco-purulent fluid, and there is generalised broncho-pneumonia. The brain is very congested; the weight is 1420 gm. There is some slight decortication on stripping the pia, which is a little thickened in the fronto-parietal region. Cortex rather atrophic in the frontal region. Fourth ventricle is granular.

Histological examination and discussion of the case.—I shall relate only the most important points and the peculiar features of the case. In the cortex of the brain I have found all the characteristic changes of general paralysis of the insane.

There was a marked lymphocyte and plasma-cell infiltration of the perivascular pial and adventitial sheaths of the vessels which exhibited proliferation and sprouting of capillaries. This was generalised in the tissue of the cortex, and there was no evidence of a gummatous wedge-shaped formation, extending from the pia-arachnoid inwards, as occurs in

meningo-encephalitis syphilitica; moreover, there was a predominance of plasma-cells over lymphocytes in the perivascular infiltration, which is more significant of general paralysis than syphilitic meningo-encephalitis in which the lymphocytes usually predominate. Some granular cells were present; in the pia there was proliferation of the fixed cell elements, with formation of large protoplasmic fibroblasts. Rod-cells (Stäbchenzellen, Alzheimer) were also present in the nervous tissue of the cortex. All the well-known changes in the neurons indicative of extensive decay of the nerve-cells and fibres were present, as well as typical changes in the glia tissue. To demonstrate the neuroglia proliferation and hyperplasia sections were stained by Heidenhain iron-hæmatoxylin and Ranke's method. The morbid histological changes were observed most markedly in the frontal lobes; the parietal lobes were affected, but to a less degree, although distinct morbid changes were observable. The left hemisphere appeared to be more affected than the right; the occipital lobes showed no distinct histological change; I found, however, very marked changes in the hippocampal region both in the grey and in the white matter. The most noticeable feature was an abundant infiltration around the vessels of almost similar intensity as was found in the frontal lobes; the right cornu ammonis seemed to be preferred, especially in the anterior part (uncus). The basal ganglia were scarcely affected; in the thalamus, however, there was some slight infiltration, chiefly in the central part. The cerebellum exhibited fairly well-marked typical changes, which I do not propose to describe here. I shall later describe the changes found in the mesencephalon and rhombencephalon; but I may now remark that in the spinal cord a typical tabetic degeneration of the posterior columns was found with exclusive involvement of the exogenous system of fibres and integrity of the endogenous systems. As the spinal cord was not so well preserved as the brain I was not able to follow the differences in degree and distribution of the degeneration in the whole length of the cord, but this principal and important feature was quite evident in preparations stained by the Weigert and Weigert-Pal methods. The Nissl method revealed a fairly diffuse chromatolysis and pigmentary degeneration of the majority of the large cells of the anterior horns, without great variations in degree in the different regions of the cord, but no vascular changes or infiltrations were noticed. Some proliferation of the ependymal cells was observed. All these changes have been described fully in previous volumes of the '*Archives of Neurology*.' Moreover, both Mott and Watson have called attention to the proliferation of the ependymal cells, which change, how-

ever, Mott has found in old non-tabetic people and in other spinal affections. Many authors have dealt with the changes in the cells of the anterior horns in general paralysis and tabes. Berger showed degenerative changes in the cells in 83 per cent. of his paralytics. The atrophy of the muscles often found in these patients and believed to be due only to inactivity or cachexia might be correlated with these changes, which do not indicate necessarily a degenerative electric reaction. Wyrnbow, Schaffer, Alzheimer, and Mott likewise mention them. Mott describes completely all the features of this lesion, and concludes that there are two possible explanations for them: either there is a superadded primary degeneration of the anterior horn-cells, or an extreme atrophy of the sensory neurons and abolition of the incidental stimuli necessary for the vital activity of those cells leads in process of time to a secondary neuronc atrophy. He considers that the second opinion is more likely to be true, because the changes in the radicular cells appear after the endogenous system of the posterior columns has been destroyed—that is, after abolition of every possible means of stimuli being carried to the cells. In the case I am describing the endogenous systems were not degenerated, yet there were degenerative changes in the cells of the anterior horns. In several cases of juvenile general paralysis which I have studied in this laboratory (an account of which was published in the 'Proceedings of the Royal Society of Medicine'), I described in one case a diffuse proliferation of glia in the anterior horns of the spinal cord in sections stained by Ranke's method. I have observed a similar proliferation in the anterior horns in this case of tabo-paralysis. It is probable that there is, then, a primary degenerative atrophy of the neurons of the anterior horns with secondary neuroglia growth similar to the primary degeneration of the cortical neurons (Schmaus and Sacki, Watson). This primary atrophy may be the result of the general toxic action of the syphilitic virus and occurs without inflammatory change.

The diagnosis of tabo-paralysis when the patient was admitted to the asylum was by no means certain. The fact that ten years had elapsed since infection supported this diagnosis, but the symptoms presented by the patient were not typical. The pupil phenomena and the ophthalmoplegia interna and externa were unlike the ordinary symptoms met with in tabo-paralysis; in fact Dr. Mott advised mercurial treatment in the belief that it was most probably a basic syphilitic gummatous process that was causing the ophthalmoplegia associated with alcoholism and a general endarteritis syphilitica to account for the mental symptoms, which in many

respects resembled Korsakow's psychosis rather than general paralysis. It might well have happened that tabes was combined with Korsakow's psychosis.

Histological changes in the fibres of the cortex.—The brains of many tabetic patients may show some atrophy of the tangential systems of fibres without any other change, and the question might be asked, Are these cases mild forms of tabo-paralysis? But an atrophy of the tangential fibres and other systems of fibres of the cortex does not necessarily denote the existence of general paralysis, for it may occur in other forms of dementia. I may add that Kaes has found a normal diminution of myelinated fibres in the cortex from forty to forty-five years of age, and that arterio-sclerosis, beginning early in syphilitics, may quicken this involution. There remain the cases of tabes with true paralysis or tabo-paralysis, concerning the onset of which I think it is unnecessary for me to speak, as it has already been treated in a masterly manner by Mott in the 'Archives of Neurology,' vol. ii. Regarding his first class of tabetic cases, with anatomically normal brains, not affected with general paralysis, but which manifested during life psychic disturbances, they correspond with Dieulafoy's "psychose tabetique." Again, Marie mentions moral and intellectual disturbances in tabetics.

Mott mentions different forms of mania and dementia in tabetics differing in the clinical characters from those of general paralysis. Alzheimer, too, points out that not every case of tabes with dementia is a general paralytic, and it is interesting to remember that in one case of his (case 21), in an old tabetic, there was a form of insanity very much like Korsakow's psychosis, but differing from my case in that no paralytic change was found in the cortex. Moreover, it is not of rare occurrence to meet with severe forms of neurasthenia in tabetics due to the effect of the combination of worry, pain, and syphilis. A consideration of these facts throws a light on the difficulty experienced in the correct diagnosis of such a case.

The pathology of tabes and general paralysis shows the unity of both diseases, there being a single morbid process with different localisations and features; thus there may occur simple tabes, *i.e.* tabes without paralytic dementia or other psychic disturbances, tabes with true paralytic symptoms and dementia in all gradations and in different combinations.

The lack of ataxia in this case is a feature which is often found in tabes when complicated by paralysis (Mott); if the ataxia exists already in such cases, the development of the cerebral affection seems to attenuate

it, by excluding "overaction" (Mott) of physiological compensations which plays a large part in the origin of ataxia. Vertigo is mentioned as a symptom in this case and is possibly due to the diplopia.

Having come to the conclusion that this is clinically and histologically a case of tabo-paralysis, we may now pass to the study of the ophthalmoplegia and of the changes in the brain which may be associated with it.

Method of investigation.—The pons and all the mesencephalon were fixed in formol, then treated for a long time with Muller's fluid, embedded in celloidin, and cut in series. On account of the friability of the material I was not able to get a complete series without gaps, but the sections permit of the study of the lesions at different levels. The sections were stained by Weigert-Pal and carmine, thionin, and Van Gieson stains. Some sections were also made from the medulla oblongata. In the latter I found the descending root of the fifth nerve and the nuclei of Goll and Burdach to be quite normal. The constant integrity of the second sensory neurons in tabes and tabo-paralysis is a point to which Mott has already called attention. The structures in the pons seemed to be normal, except in the upper portion, where I found some small hæmorrhages in the grey matter of the floor of the fourth ventricle, and some dilatation of the vessels and a slight hæmorrhagic infiltration around some of them in the nucleus of the left fourth nerve.

HISTOLOGICAL CHANGES IN THE MESENCEPHALON.

I will now pass to a consideration of the condition of the nervous structures in the mesencephalon. The medial and lateral lemniscus, as well as the pyramidal tracts, were quite normal. Between the commencing decussation of the anterior cerebellar peduncles and the here rather thin fasciculus longitudinalis posterior were scattered some cells, rather large and well preserved. I believe them to belong to the nucleus centralis superior mentioned by Obersteiner. At this level, that is, before the appearance of the nucleus of the fourth, my attention was directed to the appearance of the cells in the grey matter between the aqueduct and the fasciculus longitudinalis. There were some large cells which formed a central group in the middle and two other groups laterally: these last two soon disappeared, but the central group became more and more scattered and indistinct and became at last fused in the general appearance of the periventricular grey matter or "centrales Grau." Following the series upwards the nucleus of the

fourth appears enclosed in a dorsal furrow of the fasciculus longitudinalis posterior, and its features were so characteristic that it was not possible to confound it with other structures. The characters given by Tsuchida for distinguishing the caudal pole of the third from the fourth are very definite; the fourth has a sharper contour and it is limited from the central grey matter by a thin ridge or border of myelinated fibres; the fasciculus longitudinalis shows a deep depression for receiving the nucleus of the fourth, which is not the case for the third. Moreover, the two nuclei of the fourth are separated from each other by a greater distance than the nuclei of the third, which in the caudal pole are nearer to the middle line. Tsuchida mentions also the caudal decussation of fibres of the third as not continuing as far as the level of the fourth. All these observations are confirmed by my specimens; also the "central decussation" (Siemerling) or "medial root" (Tsuchida) of the fourth, which Tsuchida seems to consider rather rare, having found it only in a fœtus of six months and in a child of three weeks. I could make out this root very well in preparations of normal and pathological brains which I have studied. This root is formed by the fibres of the fourth, which, instead of going laterally, as happens in the majority of cases, proceeds medially along the back of the fasciculus longitudinalis perpendicularis to the bundles of the latter; near the middle line in every section can be observed a few small bundles which represent this "medial root." These fibres form probably a central connection between the nuclei of the two sides, that is, they should have the same significance as the caudal decussation of the third. Siemerling seems to admit even a direct continuation between the decussation of the third and that of the fourth. It is certain that the appearances of the medial root of the fourth are very peculiar and quite different from the decussation at the level of the third; the latter, according to Tsuchida, is more a "Durchflechtung" than a decussation of thin fibres, which are, therefore, commissural rather than radicular. The medial root of the fourth is not constant, and according to the same author does not decussate. In my specimens it shows no decussation, and consequently I am of the opinion of Tsuchida that it goes to the fasciculus prædorsalis of the same side; its further course is not known. Dorsally from the true nucleus of the fourth, beneath the aquæductus Sylvii, the grey matter shows some groups of fairly large cells, chiefly two, one on each side above and lateral to the "nucleus trochlearis"; these cells I believe to form that group, which Siemerling in his first work believed to be the nucleus of the fourth, but now he and all the authorities agree

that the fourth nucleus lies in the previously mentioned furrow of the fasciculus longitudinalis; therefore the significance of these groups is unknown. Perhaps they are not always present to the same extent owing to individual variations, which according to v. Monakow often occur in all the nuclei of this region. I should be inclined to consider this particular supra-trochlear group of cells as association neurons, connecting a part of the nuclear column of the third with the nucleus of the fourth, perhaps co-ordinating the action of the rectus inferior (third) with that of the obliquus superior (fourth).

I will now pass on to a description of the nucleus of the oculo-motor or third, which shows very severe lesions. All the structures hitherto examined were normal with the exception of some small hæmorrhages in the nucleus of the sixth, which gave rise to no clinical signs during life, the recti externi having shown no impairment in their function. Before reaching the caudal pole of the third, there were one or two sections very poor in cells; I do not think this is the result of cell atrophy, but rather the normal interval which seems to exist (Tsuchida) between the caudal pole of the third and the frontal pole of the fourth. The nucleus of the third, however, soon appears in an undoubted form in the caudal portion. The two lateral principal nuclei with their dorsal and ventral groups of cells and some elements in the middle line, which are perhaps to be referred to the posterior part of the median nucleus of Perlia, can be recognised; the cells at this level were pretty well preserved, although some destruction was evident chiefly in the dorsal group of the left lateral principal nucleus. At this level the Pal preparations show well the caudal decussation already mentioned. The network of myelinated fibres is fairly well preserved in the more ventral part of the nucleus; also the "fibræ rectæ" are seen in the middle; more dorsally the rarefaction of the network was very marked. The more we proceed in the frontal direction the more the degenerative changes were marked, the middle and the anterior part of the nuclear columns were almost destroyed, only in the ventral group some small degenerated cells were still to be seen. The nuclei of Westphall-Edinger were not seen at all; the bundles of fibres which should cross the fasciculus longitudinalis to form the roots of the oculo-motor were either attenuated or quite absent; also at the base medially from the pes pedunculi, only a very few small atrophied bundles of degenerated fibres representing the roots of the third were present. Another feature is of interest; the vessels in this region were sometimes thickened, although no profound changes were seen, not even infiltrations. They are full of

blood, and very often small hæmorrhages have taken place. It is chiefly in the middle segment of the nuclear column that this hæmorrhagic tendency was marked, and here consists not only of capillary hæmorrhages but also of larger ones. There is, therefore, in this case a degeneration of the middle and anterior part of the nuclear column of the oculo-motor, in the middle part hæmorrhagic changes predominating over simple atrophy. In the posterior or caudal part there were some changes observed but less severe in degree. The dorsal groups were more affected and the ventral better preserved. In the frontal sections I have not been able to find any trace of the nucleus of Darkschewitsch, which I suppose must be atrophied completely. It is nowadays considered as independent from the nucleus of the third; perhaps it gives origin to some part of the fasciculus longitudinalis (Edinger).

The bundles of fibres in connection with the corpora mammillaria were normal, and the fasciculus retroflexus of Meynert was well developed. In spite of the atrophy of the nuclear column of the third cells lying in the so-called grey wedge of the fasciculus longitudinalis (*grauer Keil des hinteren Strangsbündels v. Monakow*) were well preserved, as well as those scattered between the bundles of the fasciculus longitudinalis (*Buchtzellen of v. Monakow*). These two groups of cells have a different function and significance from the cells of the nuclear column. The opinions of many authors on ophthalmoplegia in tabes and general paralysis do not agree on every point. Siemerling considers the changes in the nuclei of the nerves concerned as a primary degenerative process, whilst Buzzard lays more stress on inflammatory changes. Alzheimer says that the appearances found histologically must depend upon the stage of the process; in one case he has found the same characters as in the wasted parts of the cortex, which means an actual atrophy subsequent to active inflammatory and degenerative changes. It is not even certain whether the lesion attacks the root first or the nuclei, whether the palsy is in the earlier stage fascicular and the nuclei are secondarily affected or *vice versâ*. Strumpell accounts for the transitory palsies by a radicular neuritis and a nuclear atrophy for the permanent forms. Dieulafoy, Kahler, and Dejerine are of the same opinion. Mingazzini concludes that the morbid process attacks the whole neuron, and that here, as in many other cases, the conception of the "neurone unit" is of incontestable usefulness for neuro-pathology. The nature of the changes, which are certainly nuclear in the case I am describing, is that of a chronic atrophy, probably primarily degenerative. As in Siemerling's cases, the hæmorrhages may be due to changes in the

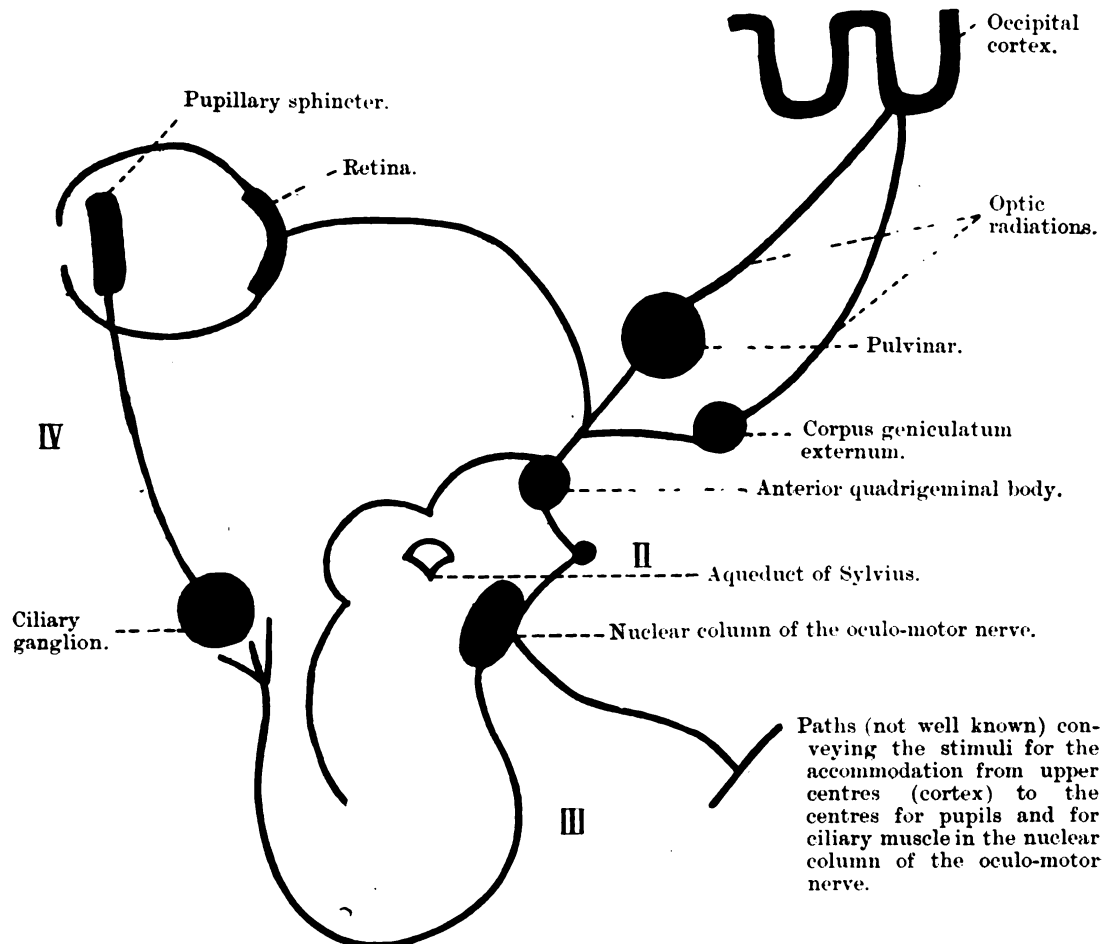
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vessel walls of the nature of arterio-sclerosis. I do not think that the changes began as an acute or subacute process comparable to those found in the cortex. I think the changes in the mesencephalon are more like those found in the anterior horns of the spinal cord.

Mott's comparative analysis of a large number of asylum and hospital cases of tabic ophthalmoplegia showed a greater number of permanent forms in his hospital cases. This was doubtless due, as he explains, to a number of cases being sent to him from the adjacent ophthalmic hospital. Garbini, in the asylum of Rome, under Mingazzini's direction, investigated this matter and found that ocular paralyses often precede paralytic dementia. According to Mott, Möbius, Swanzy, Leyden, and Goldscheider, the muscle most frequently attacked is the rectus externus; according to Charcot, and Dieulafoy, the muscles innervated by the third are generally more affected; at any rate ptosis seems to be very frequent (Iwal, Dercum). Symmetrical affection of the two eyes as in this case is comparatively rare; the common type is an *ophthalmoplegia bilateralis partialis inæqualis utriusque oculi*. It is rare to find bilateral complete paralysis of the sphincter pupillæ, which is accounted for in this case by the lesions described, which also account for the bilateral paralysis of the external muscles supplied by the motor oculi. The ptosis was more marked on the left side. The lesion seemed to be a little more marked in the left nucleus, but this is only evident in the caudal part of the nucleus, and we know that the centre for the levator palpebræ seems to be rather anterior (according to Bernheimer, Maiano, Cassierer, Schiff, Mingazzini, and Dejerine; v. Monakow, Tsuchida and Panegrossi hold a contrary opinion), and that just in the caudal part the chief decussation of radicular fibres takes place, so that slight differences in the lesions are difficult to correlate with clinical phenomena. The function of the rectus inferior was in this case the best preserved, and the part of the nucleus best preserved was caudal, which rather substantiates the opinion of Bernheimer, who puts the group of cells for the rectus inferior in the caudal sections, than that of Bach, Schwabe, Panegrossi, Tsuchida, who place this centre in the anterior part. It seems that the centre of the rectus inferior would be more likely to be as near as possible to that of the obliquus superior (fourth), that is, in the caudal pole, as we know that these two muscles generally work together in the downward movement of the eyeball, and that there are diffusely scattered cells in the nuclear column of the oculo-motor for co-ordinating movements. The downward movement of the eyeball is performed by the two mentioned muscles. It is very probable that the whole representation of this

movement lies caudal in the nucleus of the fourth and the nearest parts of the nucleus of the third, and that the groups of cells found in the periventricular grey matter above the trochlear nucleus contain the association

SCHEME OF PUPILLARY REFLEXES (SIMPLIFIED FROM V. MONAKOW).



A lesion in the IInd neuron (of the four, Ist, IInd, IIIrd, and IVth, forming the reflex arc for light) must prevent reflex to light, whereas the reflex for accommodation and the accommodation itself remain undamaged. A lesion from the nuclear column downward (IIIrd, IVth) brings suppression of every movement of the pupil. The first gives the typical Argyll-Robertson pupil; the second realises the condition of our case.

neurons responsible for the synergic action of these muscles. Concerning the innervation of the internal muscles there is a great deal of discussion amongst the principal authorities. This case throws no new light upon the subject. I can only say that the fasciculus prædorsalis and Meynert's

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commissure did not seem to be degenerated, which fact does not support the ideas of Maiano on the centres and paths of the reflex to light.

The complete palsy of the sphincter pupillæ points to a large destruction of the nucleus of the oculo-motor; the motor cells for this muscle (which send their axons to the ciliary ganglion, from which the fibres for the sphincter arise) are very likely scattered over a relatively large area along the nuclear column, perhaps more abundant in the anterior part (v. Monakow). In the usual cases of tabes or paralysis where the oculo-motor nucleus is not affected, or only slightly affected, there remain always cells enough to control the sphincter, which is not paralysed, as the reaction to accommodation shows; the lack of reaction to light is due to a lesion of the reflex arc in front of the nuclear neuron, very likely in the neuron intercalated between the termination of the optic fibres in the superficial white and grey matter of the anterior quadrigeminal body of the nuclear neuron itself; this intercalated neuron should be represented by elements scattered between the deep layers of the anterior quadrigeminal body and nuclear column (v. Monakow); and lesions in this region are fairly frequent in tabes and general paralysis (Cramer and others), and might account for the typical Argyll-Robertson sign *without* real paralysis of the pupil, whereas in my case the diffuse pupillar centre ought to be destroyed in the nuclear columns, unless lesions of the nerves and ciliary ganglion were present, which, of course, would offer another explanation (*vide* diagram).

The fasciculus longitudinalis was well preserved; it was poorer in bundles in the region of the nucleus of the third, more developed at the level of the fourth, but such a condition is quite normal (Tsichida). The fibres taking origin from the nucleus of the oculo-motor do not form the greater part of the fasciculus, and they seem to come, not from the radicular cells (true motor elements, corresponding to the large cells of the anterior horns), but from the small association elements (Schaltzellen) of the nucleus (v. Monakow, Tsichida), which are perhaps more resistant and not completely destroyed. Altogether it is not strange that the fasciculus longitudinalis shows no important changes and looks almost normal, whilst the nucleus of the third is deeply degenerated.

CONCLUSIONS.

We have a case of tabo-paralysis, the peculiar features of which are:

(A) *Clinical*.—A symptomatology very much like a Korsakow's psychosis, at least in its early stages.

An ocular palsy, all the external muscles moved by the third being affected with the exception of the recti inferiores on both sides (almost symmetrically); complete palsy of the sphincter of the pupils.

(ii) *Anatomical*.—Abundant infiltration and other paralytic changes well marked in the hippocampal region almost as much as in the frontal cortex.

Degeneration of the cells of the anterior horns of the spinal cord; the characteristic degeneration of the posterior roots and exogenous systems of the posterior columns with integrity of the endogenous systems.

Degeneration of the nuclear columns of the oculo-motor nerve, chiefly in the middle and anterior part, with some hæmorrhages; atrophy of the roots of this nerve. In the less damaged posterior part of the nucleus is supposed to lie the centre for the rectus inferior. The degeneration of the nucleus of the oculo-motor as well as of the cells of the anterior horns are supposed to be primary and without true inflammatory changes.

A well-developed "medial root" of the fourth was found.

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**Diffuse Cerebro-Spinal Syphilis terminating ten years later in
Pseudo-General Paralysis.**

By G. H. HARPER-SMITH, M.A., B.C.Cantab., M.R.C.S., L.R.C.P., and
R. W. J. PEARSON, L.R.C.P.Ed.

A MAN, aged 34 years, a horse-breaker, was admitted to Claybury Asylum, July 3rd, 1908; died July 17th, 1908. Dr. Mott obtained the following history from his wife: They had been married eight years; she had no children and no miscarriages. About eighteen months after marriage he had a fit, fell down unconscious, foamed at the mouth, and passed water. He continued on and off to have fits, sometimes slight, but occasionally severe. After some months he complained of headache, worse at night; there was drooping of the left eyelid. Then he used to complain of a numbness in his right hand and arm and weakness, which would pass off; his mouth became drawn and his speech thick; he became irritable in temper; his memory failed him; he did foolish things in consequence. He was unable to follow his business, and was admitted to the London Hospital, November 10th, 1901, under Dr. Henry Head, who kindly sent Dr. Mott the following abstract of the notes of the case: "The man contracted syphilis when he was twenty-four, and according to the father's account he had severe symptoms. Speech thick, no aphasia, no word-deafness, no headache now, but before admission he had headache in the back of the head, no vomiting, no loss of motor power, or of co-ordination.

"He is a very muscular man, both knee-jerks brisk and equal, no ankle clonus; the left great toe shows a definite tendency to extension; the right goes definitely down. There is no ptosis or ocular paralysis, no nystagmus; the face is normal; the tongue is not tremulous. Optic discs and fundi normal. Sphincters: He passed water in the bed on admission, but rapidly improved as soon as the mental state cleared up.

"*Mental state.*—On admission he was semi-comatose, and when aroused he became violent. He was always more restless at night; there are no hallucinations, no illusions, no obvious emotional disturbance. His memory has been bad lately, and has been entirely destroyed for the whole

of the present illness. He does not remember coming into the hospital; he remembers trying to get out.

"A few days after admission the delirious state with purposeless motile restlessness began to clear, and his memory for recent events improved, so much that at the end of a week the notes state—'he answered questions quite sensibly, and his mental state seemed to have cleared up.' He was discharged on December 12th, 1901.

"Diagnosis and summary.—Syphilitic cerebral endarteritis. Comatose on admission. On discharge no physical signs. He attended as an out-patient for some time, and after two months, as he improved so much, he neglected to go any more. The wife informed me that for the last six months he has been a changed man; he complained of severe headache, worse at night; there was no vomiting; waking irritable, restless states, alternated with sleepy drowsy states. For years he has been unable to do any proper work; he took no interest in anything; he had no delusions. He was a kind, affectionate husband, and up to three months ago the sexual relations were normal; since then he has been impotent. She has been married to him eight years and has had good health. Since he came out of the hospital six years ago he had been having fits; he did not lose consciousness, 'but saliva dripped from the mouth, and he lost his speech.' He was worse after a fit. He was again admitted to the London Hospital, transferred after a few days to the infirmary, and sent from the infirmary to the asylum."

His state on admission to the asylum was thus described in the notes. Heart and lungs apparently healthy. Pupils irregular and react sluggishly to light. The knee-jerks are exaggerated, ankle clonus and Babinski sign obtained. "Speech slurred and at times like a general paralytic. He is extremely confused, no idea of time, nor has he any idea of where he is or how long he has been here. He is incoherent and rambling. ? Cerebral tumour." A week later the case was diagnosed as epileptic dementia on account of the fits he was having.

July 9th, 1908.—The notes state he has marked rigidity of the left arm, leg, and side of body, with weakness of muscles of right side of face and difficulty of swallowing. No rise of temperature.

July 16th, 1908.—"He is, if anything, worse this morning; his respirations at times are slow and regular, at others quick and laboured, and Cheyne-Stokes breathing is no doubt indicated here. The next day he died."

The following is an abstract of the notes of the post-mortem examination

by Dr. Mott: "At the autopsy old basic syphilitic meningitis with universal syphilitic endarteritis cerebri was found. The whole of the cerebral vessels were affected by an endarteritis. All the arteries forming the circle of Willis show nodular or general thickening of their walls, the small arterial branches universally have the feeling and appearance of fiddle-strings, and when cut their walls are obviously so much thickened as to partially or completely obliterate the lumen. The pia-arachnoid about the base of the brain is obviously thickened, due to old meningitis. There is recent softening in both hemispheres, affecting especially the upper portion of the prefrontal and frontal regions, and corresponding to the distribution of the anterior cerebral arteries, which are thickened and occluded by endarteritis and thrombosis. The weight of the brain is 1385 gm., but the pons, cerebellum and medulla weigh together only 145 gm. instead of 175-180 gm.; no doubt this loss of weight can be accounted for by the basic meningitis and arteritis which the patient suffered with six years previously. The fourth ventricle was granular throughout. The aorta was free from atheroma except for an elongated pearly fibrous plaque just above the bifurcation."

Histological examination of the tissues.—Sections of the spinal cord at various levels were hardened in Formol-Muller fluid, fixed and cut in celloidin, and stained by the Weigert and Weigert-Pal methods.

Sections of the brain were taken from the following situations: The top of the ascending frontal, parietal, the first frontal convolutions, the basal ganglia, the pons and medulla; these sections were hardened in the same fluid as those of the spinal cord, fixed and cut in celloidin, and stained by the Weigert, Weigert-Pal, Van Gieson, and Nissl methods.

Histological changes.—The arachnoid and pia mater of the convexity are thickened owing to an infiltration of lymphocytes and plasma-cells; this infiltration extends along the septa into the substance of the brain, and is most marked in the perivascular lymphatics (see Fig. 2).

There is also a diffuse lepto-meningitis at the base of the brain, most marked in the interpeduncular space, and about the optic chiasma.

The meninges of the spinal cord show the same changes, the infiltration extending along the septa and sheaths of the small vessels (see Fig. 4).

The arteries of the brain and cord are extensively diseased; in nearly all the vessels the lumen is partially and in some cases wholly obliterated by the thickened endarterium.

In the small arteries this thickening is uniform; in the larger arteries the wall presents a nodular thickening showing on section a half-moon shape.

FIG. 1.

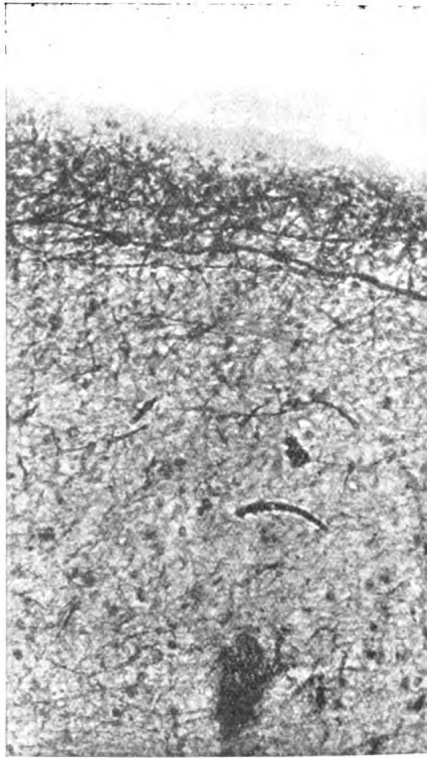


FIG. 2.

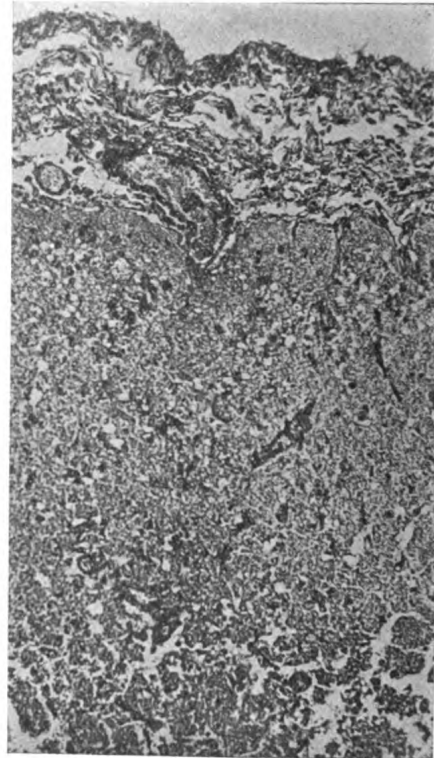


FIG. 3.

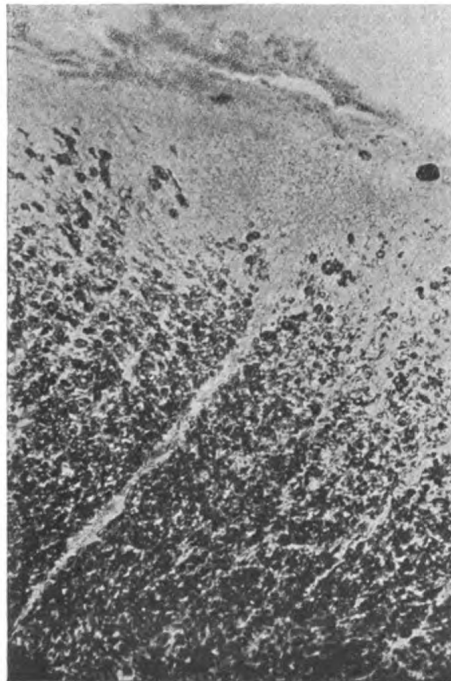
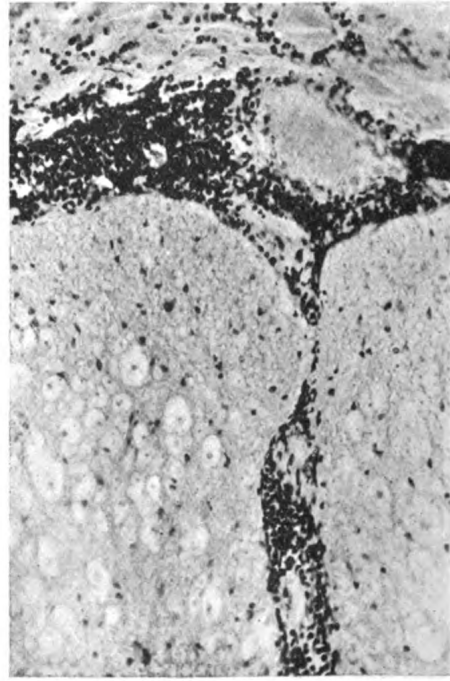


FIG. 4.



All the arteries of the circle of Willis are markedly affected, this thickening being due to a hyperplasia in the non-vascular layer, which lies between the lining endothelium and the fenestrated membrane.

Around the vasa vasorum are lymphocytes and plasma-cells; the muscular coat shows but slight changes, the nuclei do not stain deeply, and are not well differentiated (see Fig. 7).

No gummatous tumours were found in the meninges or in the substance of the brain.

In the brain there are several softenings situated in the frontal and prefrontal areas, and a large softening in the basal ganglia in the region of the lenticular nucleus of the right hemisphere (see Fig. 8).

These softenings are due to occlusion of vessels.

A section through the ascending frontal convolution stained by Nissl method shows a great increase of neuroglia with degeneration of the ganglion cells, and collection of plasma-cells round the vessels.

A section through the basal ganglia in the region of the lenticular nucleus of the right hemisphere shows increased formation of neuroglia, with destruction of nerve-fibres.

The ganglion cells of the motor area show some degeneration; in a large number of cells the nucleus is eccentric, and in some has disappeared, the Nissl granules are not distinct, and in most of the cells there is a chromatolysis.

The degeneration in these cells is not so marked as in those of the frontal and prefrontal areas.

There is a variable degree of damage to the medullated fibres; and there are several small hæmorrhages throughout the substance of the brain.

The sections of the top of the ascending frontal and parietal convolutions, stained by Weigert's method show no universal destruction of the tangential fibres (see Fig. 1); but in some of the sections there is a distinct destruction of these fibres, the membranes over these parts of the cortex being very markedly thickened, and infiltrated with small round-cells (see Fig. 2).

FIG. 1.—Motor cortex showing tangential fibres. Weigert-Pal method. Magnification 250.

FIG. 2 —Motor cortex showing thickening of meninges, and softening of the base of the section; it also shows absence of tangential fibres. Van Gieson. Magnification 85.

FIG. 3.—Section of spinal cord showing annular sclerosis — old-standing lesion. Weigert-Pal. Magnification 80.

FIG. 4 —Spinal cord showing recent small round-cell infiltration in meninges extending along the septum; it also shows old-standing sclerosis. Magnification 215.

FIG. 5.

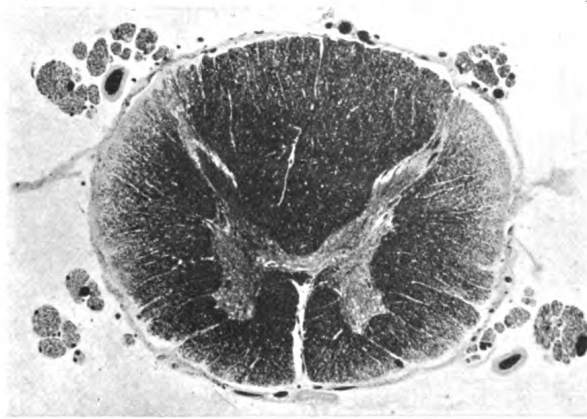


FIG. 6.

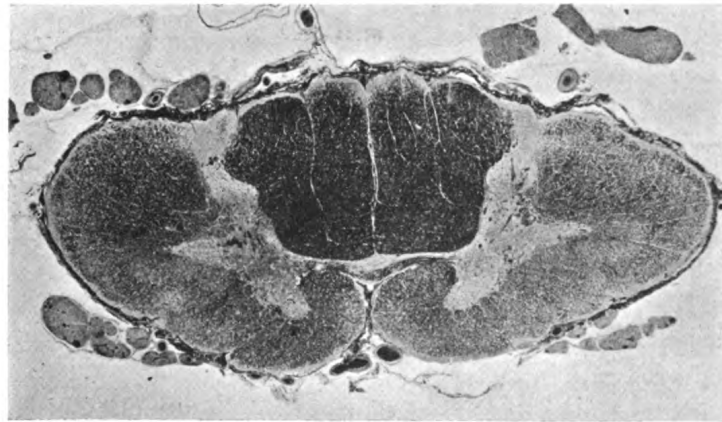
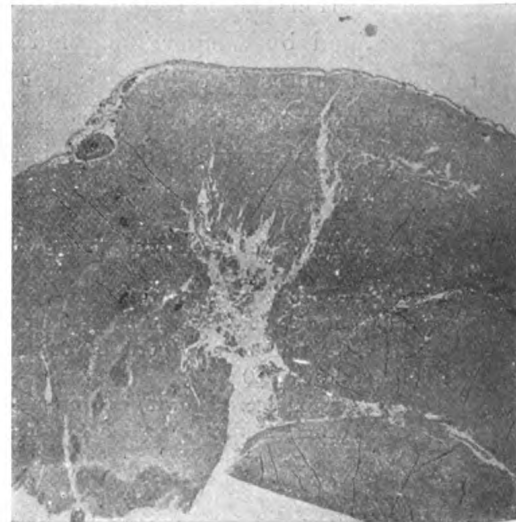


FIG. 7.



FIG. 8.



The annular sclerosis of the cord is due to an increase of the glial tissue, with a corresponding destruction of the nerve-fibres. This sclerosis was caused by the attack of syphilitic cerebro-spinal meningitis which he had six years before his death; it was a long-standing chronic condition. The sclerosis is most marked on the lateral surfaces of the cord, including the outer parts of the direct cerebellar, crossed pyramidal, and antero-lateral descending tracts (see Figs. 5 and 6). The primary degeneration of the descending tracts is owing to the old-standing sclerosis of the cortex. The columns of Goll and Burdach are almost unaffected, this being due to the fact that the thickening of the meninges and small round-celled infiltration is a much more recent development than the old-standing sclerosis of the cortex; moreover the cells of the posterior spinal ganglia, the trophic centres of the exogenous fibres of the posterior columns were not affected. This round-celled infiltration shows that the old syphilitic disease had again lit up and super-added the meningitis and infiltration to the sclerosis of the brain and cord of six years before.

In conclusion, we would express our indebtedness to Dr. Mott for his direction, help and kindly interest; and to Mr. Charles Geary for his advice on histological methods and producing the micro-photographs.

FIGS. 5, 6.—Spinal cords, dorsal and cervical regions showing old-standing annular sclerosis and recent thickening of meninges.

FIG. 7.—Artery on medulla showing endarteritis and periarteritis. Magnification 30.

FIG. 8.—Motor cortex showing softening. Magnification 15.

A Contribution to the Study of Institutional Dysentery.

By J. P. CANDLER, M.A., M.D.Cantab., D.P.H., and Professor GEORGE DEAN, M.A., M.B., C.M.Aberdeen.

INSTITUTIONAL or asylum dysentery in this country has formed the subject of several important papers, the most noticeable being the report furnished by Dr. Mott to the Asylums Committee of the London County Council.

A further criticism on this subject was published by one of us (J. P. C.) in the 'Archives of Neurology,' vol. iii, in which evidence was produced in support of the infectivity of the disease and of its similarity to the types of acute bacillary dysentery of warm climates. The close association between these two types has been proved bacteriologically by the isolation of one or other of the types of *Bacillus dysenteriae* from the stools of cases suffering from institutional dysentery both at home and abroad.

In this country Eyre in 1904 examined the faeces of five acute cases in the London County Asylum of Claybury and isolated Shiga's bacillus in four. He also isolated Shiga's bacillus in two out of four cases examined *post-mortem*. The serum of the acute cases was found to agglutinate Shiga's bacillus, but to have no effect upon that of Flexner. Further, Eyre found the Flexner bacillus in six out of nine of the acute cases above mentioned, and in fifteen out of thirty-five chronic cases. At that time he regarded the latter organism as of doubtful importance.

In 1906 one of us (J. P. C.), at the suggestion of Dr. Mott, investigated the faeces of six cases at Claybury suspected to be suffering from the acute form of the disease. In five out of the six cases the motions at the time of examination consisted of mucus and blood only; and in each case an organism resembling the Flexner type was isolated and submitted to the usual tests. In the sixth case faecal matter was mixed with mucus and blood, and from this case no organisms of the dysentery type could be isolated. This case died later and was found to be suffering from pulmonary and intestinal tuberculosis. The cultures were sent to Dr. Boycott, who was kind enough to examine them and control the results.

No organism of the Shiga type was isolated in this series. The material used for obtaining plate cultures from the fæces was the Drigalski-Conradi medium.

In 1908 a paper by Aveline, Boycott, and Macdonald was published, in which they recorded the results of a bacteriological investigation of cases of asylum dysentery. They found the *B. dysenteriae* of Flexner in the stools of seventeen out of nineteen cases of asylum dysentery. In one fatal case the spleen and mesenteric glands were alone available, *B. dysenteriae* being found in both. There was no evidence of the presence of an organism of the Shiga type in any of the cases examined.

Before relating our own findings it is necessary to refer to the work of Dr. H. de R. Morgan at the Lister Institute upon the bacteriology of summer diarrhœa in children in this country. He found (1906-07) that the *B. dysenteriae* is not responsible for the summer diarrhœa of children in London, though it has been found associated with this condition in America and elsewhere. Dr. Morgan found, however, that a certain bacillus—Morgan's No. 1 bacillus—occupied a prominent position among the non-lactose fermenting organisms in the excreta of patients suffering from summer diarrhœa. From selected cases it could be isolated in as many as 63 per cent. of the cases. The organism was found to be pathogenic to experimental animals; rats and monkeys were susceptible to infection by feeding, and after a period of diarrhœa succumbed. Dr. Morgan states that "the group to which it belongs, *i. e.* the non-mannite, non-liquefying group, is an extremely small one. The only known pathogenic member of this group is the dysentery bacillus of Shiga, which, of course, is readily distinguishable from Morgan's bacillus by at least three important characteristics, *viz.* absence of motility, absence of indol formation, and gas production."

From a small percentage of cases Morgan also isolated a bacillus which resembled the bacillus of Flexner with the exception that it produced acid with sorbite. From the small percentage of cases in which this paradysentery bacillus was found he concluded that there is no evidence that dysentery or pseudo-dysentery bacilli have any significance in the ætiology of summer diarrhœa as it is met with in London.

Details of the Investigation of Cases of Dysentery occurring at Claybury Asylum.

The material for our investigation was obtained from sixteen cases, some of which showed evidence of dysenteric lesions of the intestine after death,

while the other remaining cases were affected with dysenteric symptoms during life.

In the case of *post-mortem* material scrapings from the intestine and small pieces of the spleen were carefully emulsified in sterile broth tubes, and a few drops of the resulting emulsion were sown on to plates containing MacConkey's bile-salt lactose agar. A few drops of blood and bile from the same body were also smeared over the MacConkey plates. In all cases strict precautions were taken to obtain the material under sterile conditions.

In the case of stools obtained from living patients, those which consisted of mucus with more or less admixture with blood were treated by inseminating a small portion directly on the surface of the nutrient medium. In cases where the amount of faecal material rendered it impossible to recognise any particles of mucous material, a small portion of the stool was emulsified in a broth tube and a few drops smeared over the surface of several plates in the usual manner. The stools were in every case taken and used for examination as soon after evacuation as possible. At the end of forty-eight hours' incubation, colonies which showed absence of lactose fermentation were picked off and sown on to agar tubes. The subsequent identification of these colonies by cultural and other methods was conducted by one of us (G. D.) at the Lister Institute. The cultures were examined without reference to the numbers affixed to the tubes for identification, and in many cases it was found on tabulating the results that cultures with different numbers had originated from the same case. This method of examination, which was entirely uninfluenced by other knowledge, considerably increases the value of the results obtained, and is confirmatory of the accuracy of the methods employed.

Examination of post-mortem cases.—The following is a brief account of the cases examined and the bacteriological findings :

CASE 1: B—, female, aged 68 years. Recurrent melancholia. Large intestine showed acute ulcerative dysentery with evidence of previous chronic dysentery. The patient had suffered from symptoms of severe dysentery for over a month prior to death.

Culture tubes were inoculated from intestine, blood, bile, spleen.

Result.—Bacillus No. 1 Morgan from the intestine.

CASE 2: N—, male, aged 69 years. Senile melancholia. Acute ulcerative dysentery. This case was one of the severest types of dysentery. The whole of the large intestine was the seat of extensive dysenteric ulceration with necrosis extending into the muscular tissue. The small intestine was

extremely congested in parts, but there was no ulceration. It is interesting to note that a week prior to death this patient ceased to pass dysenteric stools and the disease was thought to have been controlled.

Culture tubes were inoculated from spleen, mesenteric gland, blood, cerebro-spinal fluid, intestine.

Result.—Bacillus No. 3 Morgan from the blood. (The cultures from the intestine in this case unfortunately died out before they could be sub-cultivated.)

CASE 3: P—, female, aged 60 years. Dementia. The intestine showed *post mortem* no evidences of catarrhal or ulcerative dysentery, but the patient was transferred to the infirmary three weeks prior to death as she was passing blood and mucus by the bowel.

Culture tubes were inoculated from the blood, bile, spleen, and intestine.

Result.—Bacillus No. 1 Morgan from the intestine.

CASE 4: E—, female. Chronic mania. This patient, one month prior to death, was noted as suffering from pyorrhœa alveolaris. One week before death she suffered from profuse diarrhœa, of an ordinary character without evidence of blood or mucus in the stool.

Post mortem: The serous surface of the intestine was covered with lymph; about one ounce of turbid, foul smelling fluid was found in the most dependent part of the pelvis. The large intestine showed intense congestion. There was a ragged ulcer invading the muscular tissue about two feet below the ileo-cæcal valve. The last eight feet of the small intestine showed intense congestion, with marked infiltration of the mucous and submucous tissue, and in places ulceration.

Culture tubes were inoculated from large and small intestine, blood, spleen, mesenteric glands, and bile.

Result.—Non-lactose fermenting organisms absent from all the cultures examined.

Probably this was not a case of ordinary dysentery, but the intestinal lesions may have resulted from infection from the gums.

CASE 5: H—, male, aged 59 years. Dementia. The mucous membrane for the distance of three inches from the anal margin presented a very marked ragged and pitted appearance, areas of ulceration being found bridged across with strands of infiltrated and œdematous mucous membrane. The condition was one of long standing. The large intestine from two to three feet above the lesion showed marked congestion of the mucous membrane. The patient never had any attacks of diarrhœa.

Culture tubes were inoculated from the ulcerated areas and from the congested mucous membrane above it.

Result.—Bacillus No. 3 Morgan in the congested area above the ulceration.

CASE 6: F—, male, aged 36 years. The whole of the large intestine was the seat of very acute ulceration. The last three feet of the small intestine were congested, with ulceration in the last six inches of its length. The patient is noted as having been subject to slight attacks of diarrhœa a short time before death.

Culture tubes were inoculated from intestine, bile, blood, liver, spleen.

Result.—Bacillus No. 1 Morgan from the spleen and bile.

CASE 7: female, aged 74 years. Senile mania. This patient was sent to the infirmary about five weeks before death, suffering from dysentery. One stool was examined five days prior to death. This was scant in character, had been passed on to the sheet and consisted of mucus tinged with blood.

Post mortem.—There was slight congestion and roughening of the mucous membrane of the lower part of the large intestine; no ulceration.

Culture tubes were inoculated from stool during life, and intestine, blood, and bile post-mortem.

Result.—From stool during life, Bacillus No. 1 Morgan; from spleen and bile, Bacillus No. 1 Morgan.

CASE 8: R—, female, aged 64 years. Melancholia. Transferred to infirmary seven days before death for slight diarrhœa. Character of stool, pea-soup consistency, semi-solid, greenish-brown, very offensive. No blood, no mucus. Two days before death only one stool was passed in the day, which was fluid, contained some mucus and blood, and was very foul-smelling. Intestine distended.

Post mortem.—The last two feet of the large intestine showed the mucous membrane to be replaced by a greenish-yellow membrane which could only be removed with difficulty from the underlying tissue. The removal of this membranous slough laid bare the muscular coat of the intestine in several places. The condition could be best described as an acute membranous inflammation of the lower bowel.

Cultures were prepared from the stools during life, and from the intestine, cerebro-spinal fluid, blood, bile, and spleen post mortem. From these situations cultures were obtained of a bacillus which could not be classified. It resembled the hog cholera bacillus of McFadyean, but did not produce any indol. No organisms of the dysentery type were found.

CASE 9: T—, female, aged 79 years. Mania. Two months before death passed two or three stools, scant in amount, mustard-yellow colour, consisting of mucus with very faint streak of blood. Stools became solid within a week (not noted as diarrhœa or dysentery).

Culture from stools: Bacillus No. 1 Morgan.

The intestines were found to be natural at the autopsy, and no cultures were taken.

CASE 10: N—, male attendant. Contracted very acute diarrhœa with rise of temperature; severe intestinal pains and vomiting. Stools light brown in colour, of thin pea-soup consistency, consisting of blood, mucus and liquid fæcal matter, becoming in the course of a few days greenish-brown, later assuming a solid form and being very offensive throughout. Patient recovered.

Cultures from the stools.

Result.—Bacillus No. 1 Morgan.

CASE 11: R—, transferred to infirmary for dysentery. Stools at first fluid, consisting of mucus streaked with blood, fairly copious, containing a little fæcal matter. In two or three days had become formed and clay-coloured; the surface streaked in places with a little blood-stained mucus.

Culture from stools: Bacillus No. 3 Morgan.

CASE 12: W. M—, noted as suffering with an attack of dysentery, from which he recovered in three weeks. Stools: Blood and mucus only at first; no fæcal matter.

Culture from stools: Bacillus No. 3 Morgan.

CASE 13: G—, male. Character of stools. Amount moderate, consistence mainly mucus with one or two small solid fæcal lumps and some streaks of blood. Stools regained normal character within three or four days.

Culture from stools: Bacillus No. 3 Morgan.

CASE 14: E—, female, aged 38 years. Admitted 1898, died 1907. Had an attack of colitis in 1898. Transferred to isolation hospital in October, 1907, with temperature of 100°F., diarrhœa with passage of blood and mucus. Patient died within a fortnight from symptoms of toxæmia due to dysentery. The stools at the onset of the attack were scanty in character, consisting of blood and mucus only. Later they became dark yellow in colour, of pea-soup consistency, and very foul smelling. The traces of blood disappeared, but there was still some mucus.

Post-mortem.—Extensive acute pulmonary tuberculosis, with old chronic phthisis. Tuberculous ulceration in the small intestine and acute ulcerative dysentery of the lower part of the large intestine.

Cultures of non-lactose fermenting bacilli were obtained from stools during life, and post-mortem from intestine, blood, bile, liver, spleen.

The cultures from this case (C. 115, C. 116, C. 118) approached closely in fermentations, etc., to the members of the dysentery group. The agglutinative relations will be dealt with in the general discussion of the bacteriological findings.

CASE 15: T—, female, aged 50 years. Put to bed on account of diarrhœa and influenza.

Stools examined, moderate in amount; one or two flakes of blood and mucus.

Result on culture of stool: No organisms of dysentery type found.

CASE 16: R—, female, aged 71 years. Transferred to infirmary as she had been passing blood *per rectum*. Stool received following day. Character very scant; consisted of a mass of gelatinous material mixed with blood. No further stools of dysenteric character passed. Patient died five months later.

Post-mortem.—Intestines normal; uterine fibroids, hæmorrhoids.

Cultures from stools: Non-lactose fermenters absent.

In summarising the clinical and pathological features of the sixteen cases described; it is doubtful if all of them can be regarded as cases of true dysentery.

In connection with certain of the cases there are points worthy of note.

In Case No. 4 the patient had been suffering from severe pyorrhœa alveolaris, and the localised ulcerations found near the ileo-cæcal valve may have been due to septic infection from the gums and mouth.

As to Cases 15 and 16 considerable doubt must be entertained as to the nature of the condition, as the stools contained blood from a doubtful source, and in the absence of definite evidence to the contrary they have been grouped with the dysentery cases.

Case No. 8 is of considerable interest. *Post-mortem*: The last 2 ft. of the large intestine showed an acute inflammatory condition of the mucous membrane with the formation of a membrane firmly attached to the underlying tissue, and leaving a granular roughened surface on removal. It will be seen from the notes on the case that the patient was sent to the infirmary for *slight* diarrhœa seven days before death, and in the interval the number of stools passed *per diem* was never excessive, though those which were passed were very foul.

No organism of the dysentery group could be isolated, but a bacillus bearing several characteristics of the hog cholera bacillus described by

McFadyean was found in the stools, the intestine, cerebro-spinal fluid, and spleen.

Control cases.—In twelve cases in which there was no previous history of diarrhœa or dysentery, scrapings were taken from the mucous membrane of the large intestine *post-mortem* and plates inseminated. In no single instance were organisms found which had any connection with the dysentery group or with Morgan's types.

Further, the stools of several cases selected at random were also investigated, and in each case the result was negative.

THE DIAGNOSIS OF ASYLUM DYSENTERY.

The diagnosis of institutional dysentery rests upon the symptoms exhibited during the attack and upon the discovery of organisms of the dysentery type in the stools.

In simple cases the diagnosis by either method is comparatively easy; in difficult cases both methods may fail, and a true diagnosis may only be reached if the patient succumbs.

Bacteriological evidence.—The routine method for examining the fæces of a suspected case is to inseminate some of the material passed, upon the surface of several plates in succession of MacConkey's bile-salt lactose agar, using for the series the same glass rod bent into an L shape, the instrument being carried from plate to plate without being sterilised. When the stool of a patient suffering from dysentery consists of mucus and blood only, there appear on the surface of the plates in the course of twelve to twenty-four hours delicate transparent colonies showing no tendency to redden the medium on which they are growing, as is the case with the lactose-fermenting organisms.

At the end of twenty-four to forty-eight hours these colonies can be picked off and sub-cultivated on to ordinary agar-agar and be subjected to the various cultural tests, including their reaction on sugar media. As, however, this method takes some days to complete, the blood-serum of the patient may be tested for its agglutinating properties towards the strain of organisms isolated from the stool, or towards a culture of the Flexner or Shiga bacillus. This method in the hands of one of us (J. P. C.) has been applied in the cases occurring at Claybury, but the results obtained were not sufficiently definite to allow an accurate diagnosis by this method. Aveline, Boycott and Macdonald have recently drawn attention to the following method of testing for agglutination, by which they claim that a

reasonably certain diagnosis may be arrived at in twenty-four hours, and afterwards confirmed by culture. For agglutinating purposes special horse-serum prepared for therapeutic use with a number of strains of dysentery bacilli was employed. The strains of dysentery bacilli included the types of Shiga, Kruse, and Flexner, those isolated by Eyre from asylum dysentery, and several from cases of infantile diarrhoea in America. This serum agglutinated the homologous organisms of the Flexner and Shiga type up to a dilution of 1 in 10,000, and was generally used diluted 1 in 1000; observations were made at room temperature.

For the actual test any suspicious colonies appearing on the MacConkey plates are picked off, cultivated in broth for four to six hours, examined for presence or absence of motility, and tested for agglutination by means of the specific horse-serum.

As an early diagnosis is desirable in all cases of dysentery, and as the various cultural tests take some days to perform, we should follow this method of Boycott in future investigations with the addition of adding the bacilli of Morgan to the strains used for horse immunisation.

From practical experience it was found that when the stool of a dysentery case consisted of mucus and blood only a very free growth of colonies of the non-lactose fermenting type took place to the almost complete exclusion of the acid formers, so that within twenty-four to forty-eight hours a very typical appearance was obtained on the MacConkey's plates which in the absence of the possibility of typhoid could lead practically to a diagnosis of dysentery. So regularly did this occur that in the absence of growth of non-lactose fermenters, from a stool consisting of mucus, or mucus and blood only, it appeared almost safe to assume that the patient was not suffering from dysentery.

The cases, then, which are most suitable bacteriologically for diagnosis, are those which present the best clinical picture of the disease, and which can easily be diagnosed without the assistance of the bacteriologist. There are, however, mild cases of dysentery unassociated with a rise of temperature or abdominal discomfort (or in which the transitory rise of temperature has been missed) in which bacteriological confirmation would be of great assistance to the clinician as an aid to diagnosis.

Such a case is seen in No. 9, an old lady who passed two or three stools, scanty in amount, and of a mustard-yellow colour, containing some mucus with a faint streak of blood. There was no constitutional disturbance, and the stools regained their normal character within a week, and remained so until she died two months later. The case was not

considered to be one of dysentery, but Morgan's bacillus No 1 was recovered from the stools. *Post mortem* the intestines appeared natural.

The following are instances in which a clinical suspicion of dysentery was negatived by the bacteriological findings.

CASE 1: An old lady (Case 16), was warded because she had been passing blood *per rectum*. One stool was examined bacteriologically. No colonies of the dysentery group were found on the MacConkey plates. The patient died five months later.

Post mortem.—No evidence of dysentery was found in the intestine, but there were internal hæmorrhoids and uterine fibroids.

CASE 2: A female was sent to the infirmary as a case of dysentery. She was stated to be passing blood and mucus by the bowel. Organisms of the dysentery group were not found. At the autopsy a few days later the intestine was found to be quite healthy, but the vagina contained a large amount of muco-purulent material caused by the presence of a large pedunculated uterine fibroid which was found protruding through the cervix.

In both these cases circumstances had prevented a thorough examination of the rectum and vagina to determine the cause and source of the discharge.

CASE 3: G—, female, aged 56 years. Recurrent mania. Five weeks before death she was stated to have suffered from diarrhœa. This continued more or less till death. Stools passed in the early stage were scanty in amount, mustard colour, grumous, no blood, slight amount of mucus. Culture of stools. No evidence of dysenteric organisms.

Post mortem.—Extensive pulmonary and intestinal tuberculosis.

CASE 4: C—, female, aged 53 years. Sent to the infirmary for an attack of dysentery. Stools relaxed, consisting of liquid material with a small quantity of fæcal matter; dark brown in colour, very offensive; a little mucus and one or two streaks of bright blood.

Six months later she vomited up some dark-coloured blood on three occasions. At the autopsy the intestines were found to be natural. Scrapings from the mucous membrane were taken, but no organisms of the dysentery group were obtained by culture. The patient died from hæmorrhage from an old gastric ulcer.

CASE 5: A. M—, female. Character of stools: Liquid contained fæcal material and a little mucus. No naked-eye evidence of blood. MacConkey's plates: All acid colonies. Tubercle bacilli were found in a film of the fæces. The case was one of pulmonary tuberculosis with diarrhœa.

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CASE 6: E. M—, female, aged 53 years. Character of stools: Liquid, contained faecal material broken up; a little mucus and shreds of intestinal mucous membrane. The case was suspected to be dysentery. MacConkey's plates: All acid colonies.

Post mortem.—Cause of death: Acute peritonitis from obstruction by a mesenteric band; perforation of small gut at point of constriction one foot above ileo-cæcal valve. Prolapse of rectum. The large intestine was free from congestion. The small intestine showed ulcerated surface close to perforation and congestion of the surrounding mucous membrane. No organisms of the dysentery group were isolated from scrapings from the mucous membrane either of the large or small intestine.

Cases similar to those above described must occasionally occur in every asylum, and it is in such instances that a negative report as regards the presence of organisms of the dysentery class might assist the clinician, and lead to the discovery of the nature of the lesion producing the change in the character of the evacuations.

The Limitations of the Method for Detecting Dysentery Organisms in the Evacuations.

As has been previously stated, the type of stool most suitable for bacteriological examination is one consisting of mucus or muens mixed with blood. Directly the character of the stool changes and faecal material becomes intermixed the greater the number of lactose-fermenting organisms which appear on the plate to the ultimate exclusion of the non-lactose fermenters. Herein unfortunately lie the limitations of the method. For in those cases in which the clinical symptoms of dysentery are somewhat obscure, and in which the motions have from the very first consisted mainly of faecal material, the isolation of non-lactose fermenters may completely fail.

Further, the difficulty of isolating organisms of the dysentery group from the formed faecal evacuations of convalescent dysentery cases and from grumous stools of chronic recurring cases, prevents to a great extent the detection of the infective and carrier cases, the proper control of which would materially diminish the incidence of the disease, for the failure to find the organisms in these cases does not exclude the probability that these organisms are still present in the mucous membrane and submucous tissues of the intestine, and only await a favourable opportunity to again light up the disease in the same patient or to become disseminated amongst others.

We have found that we have been unable to recover these organisms with any degree of certainty when the stools of acute cases have become grumous from admixture with foul-smelling faecal contents; and likewise we have failed to isolate them from the formed faecal evacuations of recovered cases. We have also failed to find them in the stools of apparently normal cases taken as controls.

This is comparable with the experience of Aveline, Boycott, and MacDonald, who examined the stools of five positive cases during convalescence with the following results. One was negative 8 and 30 days after, one negative 14 days, and two negative 25 days later.

One case also was examined as a natural control two days before the onset of dysenteric symptoms with the negative result, yet on the third day of illness *B. dysenteriae* was found in large numbers.

In three acute cases the stools failed to reveal dysentery bacilli during the acute phase; but later they were found in one of these cases during convalescence.

These observers also failed to find *B. dysenteriae* in twenty-seven control cases, though five of these had diarrhoea without clinical symptoms of dysentery.

Discussion of the Bacteriological Results obtained in the above Cases.

Several points of interest arise in connection with the results of the bacteriological examination of the cases dealt with above.

The most important is that out of sixteen cases which had symptoms of dysentery during life, or in which lesions of a dysenteric character were found after death, five yielded a group of organisms known as Morgan's bacillus No. 1, and four yielded bacilli giving the fermentations of the bacillus spoken of for convenience as Morgan's bacillus No. 3, *i. e.* a percentage of 31 per cent. of Morgan's bacillus No. 1, and a percentage of 25 per cent. of Morgan's bacillus No. 3.

It must be remarked that in the case of Morgan's bacillus No. 1 slight variations were found in the fermentations of cultures even from the same case, *e. g.* one culture would produce acid and gas in eight days, whereas another strain would produce acid and gas within two days. On the whole, however, there was a wonderful uniformity in the fermentations. As has already been stated, these observations were made without knowledge of the source of the culture, the numbers employed for cultures from the same case being frequently not in series. It was only in the final

tabulation that the relation of these numbers was ascertained. Such a method adds considerably to the value of the results.

In regard to the agglutination of Morgan's bacillus No. 1, Morgan found that the serum prepared from one strain agglutinated only a certain number of other strains. In view of this no agglutination tests have been carried out with this bacillus in the present research.

Morgan (*loc. cit.*), Eyre and Minett (1909) have found Bacillus No. 1 in a certain number of apparently healthy children, *e. g.* Eyre found it in 6 per cent. of a series of 60 cases. Two views may be taken in regard to this—either that the 6 per cent. represent “carrier” cases, or that Bacillus No. 1 is an inhabitant of the normal alimentary canal occurring in small numbers under normal conditions, but assuming an undue prominence in the intestinal flora when the conditions are made favourable by alterations occurring during diarrhœa from whatever cause.

An analogy to the latter view may be found in the occurrence of *Bacillus suispestifer* in small numbers in the alimentary canal of the healthy pig, whereas in the animal suffering from swine plague it is so abundant as to have been erroneously regarded for many years as the cause of the disease which in recent years has been proved to be due to a filter-passing organism. This illustration may serve to indicate how important it is not to draw definite conclusions as to the causal relationship in the case of the alimentary canal bacilli where the evidence rests chiefly on frequent association of the bacillus with the pathological condition.

Two of the other cases have bacilli closely allied to the Bacillus No. 3, but which differed in certain biological characters. These two bacilli, C. 116 from Case 14 and C. 88 from Case 5, prove to be of considerable interest. They produced no indol, gave the chief fermentations of the typhoid bacillus, produced acid in milk slowly, but, unlike the typhoid bacillus, were found to clot milk on the fifteenth day. They were rather readily agglutinable by anti-typhoid serum, and also in higher dilutions than usual by normal serum. They were, however, non-motile.

The first idea that occurred to us was that these might be a non-motile variety of the typhoid bacillus, but further agglutination tests have made it necessary to modify this view. Both agglutinated in 1 to 2000 “Flexner” serum, and in 1 to 20,000 “Y” serum, and in 1 to 800 by “Strong” serum. These two bacilli do not absorb “Flexner” or “Y” agglutinins from the respective sera.*

* We wish to express our thanks to Dr. J. C. G. Ledingham for his help in connection with these agglutination results.

In view of the enormous variability of the dysentery bacillus (Shiga, [1908] holds that there are at least fifteen varieties as shown by Dr. Ohno) we must regard these as probably true dysentery bacilli. The fermentations of these two bacilli and the other dysentery bacilli, Morgan's No. 3, are shown on the table.

The bacilli from Cases 11 and 12 were not agglutinated by "Flexner" nor "Y" nor "Strong" serum. A second race from Case 12 was agglutinated by "Y" serum in a dilution of 1 in 200. The two strains from Case 12 were agglutinated by serum prepared from C. 81 from Case 11, but were not absorbed by C. 81 agglutinins.

The failure to obtain cultures of a bacillus giving all the characters of the true Shiga or Flexner bacilli in any of the above cases is noteworthy and difficult of explanation.

It must, however, be stated that whereas in some of the cases the majority of the colonies which appeared on the MacConkey plates were non-lactose fermenters, and a large number of which were picked off and transplanted on to slopes of agar-agar, some of these unfortunately died out before they could be examined fully. It is possible, therefore, that some of these more delicate colonies may have been those of the true Shiga or Flexner bacilli. In many of the cases, however, we are quite certain that no colonies of the true "Flexner" variety appeared on the plates.

It is particularly interesting to note that within the last few years the number of cases of dysentery in the asylum at Claybury and the severity of the attacks have markedly decreased, and owing to the preventive measures taken an outbreak of dysentery is rare, and the number of cases found with dysenteric lesions at autopsy has considerably decreased. This change was already in evidence when the above investigations were conducted. It is possible, therefore, that the "Flexner" type of organism has died out *pari passu* with the more acute form of the disease, and that its place has been taken by the organism described by Dr. Morgan, and which he has shown to be associated with summer diarrhoea in children. At any rate, in the light of our own researches we venture to suggest that the two types of organisms described by Morgan must be added to the group of organisms associated with, and possibly responsible for, some of the cases of dysentery met with in asylums.

Conclusion.—The object of this paper is to report the presence in certain cases of intestinal dysentery at the London County Asylum at Claybury of types of organisms which have been associated by Dr. Morgan with the summer diarrhoea of children.

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Some of the difficulties and conditions leading to error in the clinical and bacteriological diagnosis of institutional dysentery have been indicated, and attention drawn to the usefulness to the clinician of bacteriological methods. The limitations in practice of such bacteriological methods are discussed in the light of our experience.

Table Showing the Fermentations, etc., of the Chief Groups of Organisms Isolated and of the Well-known Types to which they are Related.

Bacillus.	Motility.	Arabinose.	Glucose.	Lavulose.	Galactose.	Maltose.	Saccharose.	Lactose.	Raffinose.	Inulin.	Dextrin.	Salicin.	Erythrite.	Sorbitol.	Mannite.	Dulcitol.	Milk.		Indol.
																	Two days.	Eight days.	
Dysentery (Shiga)	—	—	A	A	A	—	—	—	—	—	A S	—	A S	—	—	—	—	{ Alk	—
Dysentery (Flexner).	—	A	A	A	A	A	—	—	A S	—	A	—	—	—	A	—	A	{ Alk	+
Morgan I	+	—	AG	AG	AG	—	—	—	—	—	—	—	—	—	—	—	—	{ Alk	+
Morgan III.	—	A	A	A	A	A	—	—	—	—	A	—	—	A	A	—	A	A	+
B. Hog - cholera (McFadyean).	+	AG	AG	AG	AG	AG	—	—	—	—	AG	—	—	—	—	—	A	A	+
Case 3 (six strains)	+	—	AG	AG	AG	—	—	—	—	—	—	—	—	—	—	—	—	Alk	+
Case 10 (four strains)	+	—	AG	AG	AG	—	—	—	—	—	—	—	—	—	—	—	—	—	+
Case 7 (seven strains)	+	—	AG	AG	AG	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Case 6 (two strains)	+	—	AG	AG	AG	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Case 9 (one strain)	+	—	AG	AG	AG	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Case 8 (four strains)	+	—	AG	A	AG	—	—	—	—	—	—	—	—	—	—	—	A	A	—
Case 12 (three strains)	—	—	A	A	A	—	—	—	—	—	—	—	—	A	A	—	SA	—	+
Case 2 (one strain)	?	A	A	A	A	A	—	—	—	—	—	—	—	A	—	—	SA	—	+
Case 11 (two strains)	—	—	A	A	A	A	—	—	—	—	—	—	—	A	A	—	A	—	+
Case 13 (one strain)	—	—	A	A	A	A	—	—	—	—	—	—	—	A	A	—	AS	—	+
Case 5 (three strains)	—	A	A	A	A	A S	—	—	—	—	—	—	—	—	A	—	A and C	—	—
Case 14 (three strains)	—	A	A	A	A	A	—	—	—	—	—	—	—	—	A	—	A and C	—	—

A = Acid. G = Gas. S = Slight. — = No recognised change in medium. Where particular tests not carried out, as under sorbitol, a blank is left. Alk = Alkaline. C = Clot.

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The Psychological Conception of Insanity.

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PSYCHIATRY has been throughout its history the victim of innumerable conflicts of opinion. These conflicts have related not only to questions of fact and theory, but to the very groundwork of the science—the material with which it deals, and the proper methods of research by which it should be approached. A science constructed upon a shifting basis can have no stability or permanence—and therefore psychiatry has had but little share in the triumphal progress of its sister sciences.

If we glance through the history of psychiatry we see a succession of revolutions—the rapid replacement of one mode of conception by another, and the abandonment of almost every result to which the former mode had led. We see the singularly enlightened conceptions of the Greeks replaced by the theological conceptions of the middle ages, and the development of the view that the symptoms of insanity are the manifestations of an evil spirit lodged in the body of the patient. Such a conception led logically to suitable methods of diagnosis, the procedures of the witch trials, and to suitable therapeutics, the exorcising of the offending devil, or the burning of the witch.

This hopeless confusion of the categories, of the material and supernatural, the psychological and moral, was obviously incapable of yielding any satisfactory results, and men turned expectantly to that new method which was revolutionising human knowledge, the method of the natural sciences. But this method had hitherto only concerned itself with the material world, and the endeavour to bring psychiatry within the pale led to the postulate that the basis of mind is brain, and that insanity is a disease of the brain. Around this postulate arose the physiological conception of insanity, a conception of the utmost historical importance, and one which has, until within recent years, dominated almost the whole field of psychiatry. Even at the present day many authorities are convinced that any attempt to deal with the problem of insanity from the

point of view of psychology is doomed to failure, and that the therapeutics of the future will be inevitably limited to the methods of physiology and physiological chemistry. Some even deny that psychology can form a portion of science, that it deals with material which can be treated by the scientific method, and they insist that mental processes must first be translated into physiological terms before we can attain to any exact knowledge of their laws and causation. This school has been aptly described by Höfding as virtually wishing to abolish psychology in order to make it into a science.

Notwithstanding this destructive criticism the psychological conception of insanity persisted in asserting its vitality. It has passed through a long sterile period, dominated by the introspective psychology of former days, a period whose meagre results justified to a large extent the contempt of the practically minded physiologist. It was thought that the methods of the natural sciences were not applicable to psychology, and these were therefore replaced by armchair speculation which bore no resemblance to the procedure adopted in other branches of knowledge. And yet the futility of an attempt to understand *dementia præcox* by means of analogies from introspection hardly requires demonstration.

In recent years, however, psychological psychiatry has made gigantic strides—it has discovered that the mind can be treated as a phenomenon, and can, therefore, be rendered amenable to the method by which we study all other phenomena—the method of science. The recognition of this simple fact has led on the one hand to the introduction of experimental psychology, and on the other to the immensely important work of Janet, Freud, and Jung. The psychological conception of insanity has acquired a new life, and now offers, we believe, the most fruitful method of modern psychiatry.

It is not difficult to trace to its roots the dogmatic assertion of certain authorities that the physiology of the brain is the only profitable method in psychiatry. It rests upon a crude and naïve conception of the nature of reality and of science. Reality is regarded as something extended, tangible, and visible, and science is assumed to be concerned with measurement, and, therefore, only applicable to the material world. The brain constitutes a part of reality, something which really exists and is causally effective, whereas psychological research is concerned with flimsy unrealities. Science cannot deal with unrealities, and must, therefore, limit itself to an external “real” world of “things in themselves,” composed of extended objects arranged in an infinite space. This is the

doctrine that aroused Mach's gibe that "The majority of natural scientists tend to embrace a materialism some hundred and fifty years old, whose insufficiency has long been obvious, not only to the philosophers proper, but to all those accustomed to think philosophically." (1)

This crude theory of the physiological dogmatist extended in former days over the whole field of science. Scientists had concerned themselves solely with the search for knowledge and did not consider the foundations upon which they were building. During the nineteenth century, however, a school of critical philosophy arose devoted to an investigation of the bases and nature of science. Owing to the labours of Clerk-Maxwell (2), Ostwald (3), Mach (4), Karl Pearson (5), and other members of this school the method of science has now been precisely formulated. The nature of this method has been most perfectly described in Pearson's classical 'Grammar of Science.' Limits of space prevent more than a short summary of the principal conclusions reached therein—for the demonstration of their validity the reader must be referred to the original work. These conclusions may be stated as follows: Science is characterised solely by its method, not by its material. It is, therefore, applicable to the whole field of human experience. It deals with *phenomena*, not with "things in themselves," "matter," or other metaphysical abstractions. Its method is, firstly, to classify phenomena into sequences; secondly, to find some general law which will enable us to resume these sequences in a short and convenient formula. These laws are constructions of the mind and form no part of phenomenal experience—in other words, they are conceptual in character. The justification of a scientific law consists solely in the fact that it enables us to resume and predict our experience. Thus, in order to explain the phenomena of chemistry, we construct the conceptual atomic theory. The scientist may be compelled, not only to construct the law, but to invent the objects between which the law is conceived to hold. Atoms have not been seen, or heard, or touched; they are not phenomena, they have been invented by the chemist. The chemist has, in fact, constructed a conceptual model of the universe: his claim is merely that by the aid of this model he can deduce certain results, and that these results will be found to agree with the phenomena actually occurring in nature. The physicist has adopted a precisely similar method, and makes a precisely similar claim with regard to the phenomena of light and the theory of ether waves. The conceptual models of the scientists are not only non-phenomenal; they may even contain elements which contradict all phenomenal experience—

for example, the weightless frictionless ether. The method of science, therefore, consists in (1) the observation and classification of phenomena, (2) the construction, by the aid of the disciplined imagination, of a conceptual model designed to resume these phenomena, (3) the comparison of the results deduced from this model with the facts of actual experience. The last step establishes the validity of the conception; if this test is not satisfied the conception is merely a useless phantasy.

Underlying all these principles is the distinction between the phenomenal and conceptual, and it is of fundamental importance that this distinction should be clearly understood. Our actual experience is phenomenal, and every fact of experience is regarded by science as a phenomenon. A conception, on the other hand, is a construction of the human mind, and it forms no part of phenomenal experience. Thus colour is a phenomenon, the ether and its waves are conceptions. Similarly, chemical substances, moving bodies, and nerve-fibres are phenomena—atoms, force, and nerve-currents are conceptions. The modern scientist no longer imagines that atoms and ether waves are phenomenal realities; he will at once acknowledge that he has invented them in order to explain his phenomenal experience.

Now, if science is concerned with the whole field of human experience, it must be applicable to mental phenomena, for surely the mental is as much a portion of human experience as the material. And if science aims at the construction of a conceptual model designed to resume our experience, it cannot be synonymous with measurement—measurement must be merely one of the means by which this aim is attained.

Let us next consider how science deals with this problem of the physical and mental. If we inquire of the physicist where he places mental phenomena in his scheme of the universe, he replies that he does not place them anywhere, and that their introduction into his chain of cause and effect would altogether vitiate his conceptions. He insists that the physical world must be regarded as a closed series in which the psychical plays no part whatever. If we turn to the physiologist we are no better off: he is willing to deal with psychical phenomena if we will allow him to translate them into complicated interactions of nerve-cells and fibres, but with the psychical in itself he has no concern. Are we, then, to conclude that the psychical is a mere epiphenomenon, something which has no place in the universe of the scientist? Surely not, for if the psychical is a portion of human experience it must be amenable to the method of science. The difficulty is solved by the introduction, as a

working hypothesis, of the doctrine of parallelism. The psychical and the material form two series ; within each the law of causation is effective, but between the two there is no causal relation. Ideas may be causally related to other ideas, and molecules may be causally related to other molecules, but an idea cannot cause a molecule, nor a molecule an idea.

Science is compelled to make this assumption because it cannot construct useful concepts unless the physical and psychical series are kept rigidly apart. It does not need to establish parallelism as an absolute truth, nor need it concern itself with metaphysical problems concerning the relation of mind and body. Human experience may be regarded from two aspects: from the psychical point of view it is a chain of phenomena conceived as forming part of a consciousness ; from the physical point of view it is a chain of phenomena conceived as occurring in space, and forming part of a physical universe. In other words we may say that the physicist resumes his experience by means of a conceptual model involving space and time, whereas the psychologist regards it as the chain of mental factors constituting a consciousness. The ultimate goal of the physicist is a complete description of the universe in terms of motion or mechanism ; the ultimate goal of the psychologist is "personality."

Science is compelled to treat the physical and psychical series rigidly apart because, as we have seen, the doctrine of parallelism demands that no causal relation between elements of the two series shall be postulated. This principle has long been realised by the physiologist. He refuses to introduce psychical conceptions into his chain of cause and effect—his aim is to construct a conceptual model composed entirely of physiological elements. The psychologist, however, rarely grasps the full significance of the principle of parallelism, and he is often content to fill up the gaps in the psychical series with cells and nerve-currents. It is this confusion of the categories which has so retarded the progress of psychology in comparison with that of its sister sciences. So long as this confusion is not realised psychology cannot proceed to that second step which we have described in our preliminary exposition of the method of science. It will remain a mere description and classification of phenomena, and will be unable to attempt the construction of a conceptual model designed to resume those phenomena.

The principle of parallelism demands, therefore, that psychology should be excluded from physiology, and as a necessary corollary that physiology should be excluded from psychology. The psychologist must refrain from introducing physical terms into his chain of cause and effect. Now this

proposal immediately arouses considerable practical difficulties—and it certainly requires some qualification. It will be objected, for example, that the clinical method largely depends upon this alleged confusion of the categories. We know that if we give a quantity of alcohol to a certain individual he will develop a certain mental state characterised by a peculiar clouding of consciousness, etc. Are we, then, talking nonsense when we say that the alcohol causes this mental effect? The solution of this apparent dilemma lies in the ambiguous use of the word “causation.”

Höffding states that “the causal concept appears under two aspects: under a provisional elementary form, with which we are often compelled to be contented; and under an ideal aspect which all research and all theories strive after. The elementary causal concept presents only an unconditional succession; if the phenomenon A appears, then B inevitably follows, and B only appears when A has preceded it. The ideal causal concept goes a step further and sees in the phenomenon which we call the consequence the continuation of that phenomenon which we call the cause or its equivalent in a new form.” (6) Thus, when we say that the tubercle bacillus is the cause of phthisis we mean that the bacillus is an invariable antecedent of the disease—this is an example of the first or empirical type of causation. When, on the other hand, we say that heat is the cause of motion, we mean that motion is the equivalent of heat in a new form. Heat is conceived as being the vibration of particles, and hence motion can be regarded as a continuation of the same phenomenon. This is an example of the second or ideal type of causation.

It will be found that this second or ideal causation is only met with upon the conceptual plane, never upon the phenomenal. Upon the phenomenal plane we experience only a succession of phenomena—hence it is that mere observation of the facts of experience will only yield us that form of knowledge which we term “empirical.” Empirical knowledge is, in fact, the result obtained by the application to our experience of the elementary causal concept; it is that observation and classification of sequences of phenomena which we found to be the first step in the method of science. Such knowledge is rightly regarded as merely preliminary in character, and science is not satisfied until it has proceeded to the ideal concept of causation. Thus when Kepler demonstrated the fact that a planet would be in a certain position at a certain time because it moved round the sun in an ellipse, he was employing the elementary causal concept. Newton, however, went further, and succeeding in explaining the same fact by means of his conceptual model of particles

attracted towards each other by the force of gravity, thereby employing, of course, the ideal concept of causation. It is this ideal concept which constitutes the "why" of science, whereas the unconditional succession of phenomena is merely the "how."

This ideal concept of causation is only to be found upon the conceptual plane, and it is only by means of a conceptual model that we can ever "explain" our experience. That aspect of continuation, of equivalence in a new form, is never found upon the plane of our phenomenal experience; it is a result only to be achieved by the efforts of our constructive imagination.

Our final conclusion is, therefore, that while in our preliminary classification of phenomena it is admissible to employ terms from both the physical and psychical series, such a procedure is altogether inadmissible when we proceed to the second step of the method of science, the construction of a conceptual model designed to explain the phenomena. The terms of a scientific conception must always be taken from one or the other series, never from both. For otherwise it would be obviously impossible to obtain a "continuation" and "equivalence in a new form." Thus the physiologist is prepared to accept as a first approximation our statement that the idea of a good dinner causes our mouths to water. But when he proceeds to the construction of his conceptual model our statement will be discarded, and he will produce only a picture of cells and fibres, traversed by nerve-currents, and obeying only physiological laws.

We are now in a position to return to our original dilemma concerning alcohol and mental confusion. When we say that alcohol causes mental confusion it is obvious that we are employing the term "cause" in its empirical sense; we are merely registering the fact of observation that administration of alcohol is followed by the phenomenon of mental confusion. The second phenomenon cannot be regarded as the equivalent of the first—it is altogether impossible even to conceive mental confusion as the equivalent of alcohol in a new form.

It must be clearly understood, of course, that empirical knowledge of this kind is far from useless. It is a very valuable first approximation, not only useful in itself, but serving to indicate the lines along which further research may be profitably undertaken.

We may therefore qualify our original statement as follows: The psychologist is at liberty to introduce physiological terms into his subject so long as he makes no effort to proceed beyond the limits of a merely

descriptive science. But if he desires to bring psychology into line with the natural sciences he will be compelled to introduce the conceptual method. He must then clearly understand that the introduction of physiological elements into conceptual psychology is inadmissible, and that he must altogether confine himself to the psychical series.

Let us now endeavour to apply these principles to the study of psychiatry from the standpoint of psychology. Firstly, the phenomena must be accurately observed and classified. This necessary first step was in former days rendered impossible by the predominance in psychology of the introspective method, for introspection was obviously inapplicable to the mental processes of the insane. It was only with the introduction of an objective psychology that the facts of insanity could be rendered amenable to scientific observation. Objective psychology depends upon that process of deduction from analogy which we customarily employ in everyday life. We have no immediate knowledge of any consciousness but our own; we deduce the consciousness of others in one of two ways—either directly from what they tell us by means of speech, or indirectly from certain actions they exhibit, actions which are invariably connected in ourselves with certain conscious states. By these modes of observations we are enabled to describe and classify the sequences of mental phenomena which occur in the mind of another person. In precisely the same way we can describe and classify the sequences of mental phenomena which occur in the mind of a lunatic. It must be admitted, of course, that in this second case the sequences may be more fragmentary, because we are frequently compelled to depend mainly upon our deductions from the actions of the patient, and only to a small extent upon his verbal communications.

As a result of work conducted along these lines a considerable body of psychological material has been collected, and this material has been to some extent classified. The process has been carried out in the sphere of both normal and abnormal psychology. As an example of such observation and classification in the latter sphere we may cite the dissociations of consciousness demonstrated by the French school during the latter half of the nineteenth century, in particular the work of Janet upon the sub-conscious phenomena of hysteria. Further research has revealed the fact that the operation of dissociation can be traced throughout the whole range of the normal and abnormal mind—from the “habits” of everyday life to the hallucinated voices of the paranoiac.

The minute analysis of the phenomena of the mind formerly occupied

the psychologist to the exclusion of every other aim, owing, we believe, to the erroneous view that no conceptual psychology was possible until the mental phenomena had been dissected into their ultimate elements. It is not disputed that accurate observation and classification of facts are a necessary preliminary to the employment of the conceptual method, but the complete analysis of each phenomenon into its structural constituents is by no means essential. Thus Newton formulated the laws which govern the interactions between particles at a period when the analysis of these particles into their chemical elements was in its infancy.

We may now proceed to inquire what use psychology has hitherto made of this conceptual method, what progress is at present taking place in this direction, and therefore to what extent psychology has now advanced beyond the standpoint of a descriptive science. A cursory examination of the facts will at once convince us that conceptualisation of a simple unsystematised type has been employed by the human mind from the very beginning of its history. "Memory," for example, is such a concept. We are only actually cognisant of the fact that a certain mental event is liable to recur at some subsequent time. In order to satisfy our demand for continuity we assume that this mental process must somehow have existed during the interval, and we construct the concept of "memory" in order to explain this continued existence. Similar simple concepts can be found throughout the whole range of popular psychology. Nineteenth century physiological dogmatism refused to admit that these conceptions had any claim to be incorporated into science. It insisted that the mental process had no psychical existence during the interval in which it was not being actually experienced, and that "memory" was for science nothing but the persistence of physiological traces in the brain. This view involves that confusion of the phenomenal and conceptual and that confusion between the physiological and psychological series which we have already seen to be destructive of all coherent science. Firstly, the physiological brain-trace is not a phenomenon—it is made up of such conceptual constructions as "nervous energy" and "permeability of paths," and is therefore itself a conception, and not a fact of experience. Secondly such a physiological conception, while admirably adapted to explain the connection between two successively appearing brain facts, is altogether unadapted to explain the connection between two mental events. We cannot conceive one mental event as continuously passing over into the other if the intermediate links are composed of such disparate stuff as nerve-cells and fibres. But it is just this "continuous passing over" which we achieve by the construction

of our psychological conception of "memory." Once it is definitely realised that the physiological "brain-trace" is as much a conceptual abstraction as the psychological "memory," and that neither are to be regarded as phenomena, the superior claims of the latter, when we are speaking of psychical events and not of physiological events become immediately obvious.

We owe to Professor Freud (7), of Vienna, the first consistent attempt to construct a conceptual psychology on lines similar to those which have proved so successful in other sciences. He devised the conception of the "unconscious," and endeavoured to explain our actual conscious experiences as the result of mental processes of which we are altogether unaware.* This conception has been systematically developed both by its original author and by the school of which he has been the founder. Whatever view one may take of certain of Freud's developments, it must now be admitted, we believe, that the essential groundwork of his theory has been definitely established.

A description of these methods and theories does not, of course, lie within the scope of this paper. Our purpose is merely to indicate the broad lines of their historical development, and the importance which they have now acquired in modern psychology. Freud's investigations were primarily directed to the study of the neuroses, and in particular to the psychological aspects of hysteria. By the employment of his method of "psycho-analysis" he found that the symptoms of hysteria could all be explained as the result of an emotional conflict. A certain system of ideas, which was for some reason incompatible with the personality, was repressed into the unconscious, and the patient became henceforth unaware of its existence. It continued, however, to exert in various indirect ways an effect upon the personal consciousness—these indirect effects constituted the symptoms of hysteria. The laws by which the hysterical processes proceeded were found to be identical with those governing the processes of normal life. Dr. C. G. Jung (8), of Zurich, continued the work of investigation. In his well-known 'Diagnostische Assoziationsstudien' he confirmed Freud's

* Hartmann's original conception of the "unconscious mind," though similar in form, was constructed on lines opposed to the method of science. It endeavoured to explain everything, and therefore succeeded in explaining nothing: its relation to Freud's theory is merely one of superficial resemblance. See two articles by the present author, "A Philosophy of Psychiatry," 'Journal of Mental Science,' July, 1908; and "The Conception of the Subconscious," 'Journal of Abnormal Psychology,' 1910. These contain a more complete discussion of the general principles constituting the scientific basis of psychiatry, and the reader is referred thereto should the descriptions contained in the present paper not be sufficiently clear.

results, and demonstrated that the labour of psycho-analysis could be considerably shortened by the use of preliminary association experiments. He also extended Freud's method to the study of dementia præcox from the psychological aspect, and showed that the same essential mechanisms were to be found here as in the case of hysteria.

Considering the short period during which these investigations have been in progress the results have been astonishingly fruitful, and we are now within measurable distance of a psychological conception of insanity. Much work is still needed, but the future is bright, and we may reasonably look forward to the establishment of a psychiatry worthy of the name of Science.

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Two Cases of "Washing-Hand" Mania, with some Observations on their Etiology.

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IN the progress of our knowledge of psychiatry no more important advance has been made than that which depends upon the realisation that the phenomena of mental diseases are subject to the same laws as those which govern the processes of the normal mind, and that the disease syndromes which are so familiar under the various labels of an ever-changing nomenclature are really the outcome of the gradual influence of certain morbid factors upon the whole development of the personality. The two cases of obsession-impulsion described below will, I think, emphasize these points, and in the study of their evolution appears to lie the principal indication of their etiology.

Caroline M—, single, aged 31 years, was admitted into the asylum in November, 1908. She was suffering from mental depression together with ideas of unworthiness, and an uncontrollable impulse to wash her hands. Prior to her birth her mother had been in a very weak state of health. Her previous history revealed the fact that she had been backward and slow in development; at school she attained to the sixth standard, and she was then brought up to domestic service. She has been in several good situations, and appears to have possessed ordinary intelligence and ability. In early life she suffered much from erytrophobia. She was peculiarly timid and sensitive in disposition, and although she was aware of her practical usefulness in her own sphere of work, she was nevertheless over-ready to disparage herself, and frequently experienced a feeling of incapacity, especially when placed in unusual circumstances. She was extremely conscientious, but lacked self-confidence. Her inability to make up her mind and act with decision caused her to depend unduly upon the direction of others. She was retiring and reserved, and made no very intimate friends. Unambitious and simple in her ideas and desires, she gave much thought to religion, and was unduly

impressed with the idea that her normal sexual feeling was something to be ashamed of and suppressed. While her earlier life had not been unhappy, it was nevertheless colourless and devoid of satisfaction, and she grew up to be self-centred and secretly discontented. No serious love affair appears to have ever disturbed the monotony of her life. Her attention was expended in matters of small consequence, and in an exaggerated punctiliousness.

Five years previously, when in service, curiosity respecting the nozzle of a douching apparatus belonging to her mistress led her to give way to experiments upon herself, which developed the habit of masturbation. In the course of time, however, remorse and disgust at herself enabled her to overcome this practice, the painful memory of which she more or less succeeded in putting away from her mind. Nevertheless, in the process of this suppression she experienced feelings of profound shame and personal unworthiness, an experience which left an indelible mark on her personality.

At her last situation (June, 1908) she was suffering from menorrhagia. Her linen was much stained, and this incident worried her excessively because she thought that her fellow-servants would remark on it. She was habitually clean in her habits, and the opposing idea of uncleanness, as I hope to demonstrate, already exercised a morbid influence on her personality. At this time there occurred a case of infectious illness in the household, and it was part of her duty to handle a quantity of soiled and infected linen. This was an additional source of anxiety to her; it was something unusual which she was called upon to cope with, and instead of reacting to this fresh call upon her energy the feeling of incompetence inherent in her disposition was accentuated. The next step was the insidious growth in her mind of doubts and questionings about her personal cleanliness, and she reacted by making unusual efforts to wash herself on every possible occasion. This habit became an impulsion over which she was less and less able to exercise any control.

Her habit of observing and discussing with herself each little detail of her methods led her into interminable self examinations: thus, having washed some article with great care, she would then wash her hands, and after drying them with a towel, she would commence questioning herself as to whether anyone else had used the towel, and if so, whether her hands were not again soiled. She would then laboriously repeat the washing process, and having at length temporarily satisfied her mind, doubts would arise as to whether perchance she had or had not contaminated the towel, and if so, might it not come about that someone else would use this towel and so

become infected through her. She developed a dread of touching any object of wearing apparel, and was gradually reduced to such a helpless state of hesitation and doubt that she was quite unfit for her work, and voluntarily came to the asylum.

She was a woman of small stature, somewhat ungainly in build, with rather heavy features and a coarse skin. There was a growth of hair on the upper lip. Her general health and condition was fairly good and the reflexes and sensation were normal. No history of neuropathic heredity was obtained. She was very quiet in manner; her expression was as a rule calm, but her eyes were red as with weeping and she was over-readily emotional. She replied at once to my questions and willingly gave a very good history of herself; there was no appreciable retardation. She appeared well orientated and quite realised her position and circumstances; her memory was unimpaired. She conversed intelligently and rationally on such topics as she was interested in and which did not awaken any morbid affect in her mind; but the attention was generally centred upon the depressing content of her thoughts, of which after some preliminary hesitation she spoke openly. There was a strongly subjective feeling of incapacity and incompleteness. She was morbidly cognisant of her own timid and retiring disposition, and told me that she had always experienced a difficulty in making a decision where her own interests were concerned, and that she was seldom free from the consciousness of effort in her daily life. There was no generalised or marked depression, she occasionally smiled in speaking of her past life, and could be distracted from the influence of the distressing thoughts which tended to dominate her mind; she told me that she felt wicked and unworthy and that she must be guilty of sin. She was unable to rid her mind of the idea that she was unclean; this idea dominated her attention and was the theme of an unending argument or rumination, which only ceased when she obtained sleep, but the feeling of anxiety and doubt recommenced on waking. Sleep was broken and seldom brought her complete mental rest.

She complained of her inability to stop washing her hands and that she could not get rid of the idea that they were dirty; this idea forced itself upon her but she retained her power of forming a sane judgment upon it and recognised that it was something abnormal in herself and that her action in washing her hands in this way was irrational. The continued contest that was carried on with this obsessive idea absorbed the greater part of her mental energy. There was a prevailing affect of anxiety with feelings of incapacity and of dissatisfaction. She would reproach herself in

everything she had done or left undone ; the idea of personal wickedness was out of all proportion with the facts of her history, and this, on argument, she admitted to. Finally she confessed to her former habit of masturbation.

She would constantly revert to disparaging thoughts concerning her work and maintain that such work as she did accomplish was badly done and this despite all evidence to the contrary. She was in this way morbidly critical about herself ; nevertheless she was not without insight into her condition, which she recognised as strange and abnormal ; but unless forcibly held in conversation or driven to employment she would lose all practical grasp of reality. Left to herself she became restless and agitated or had definite though mild crises of diffuse anxiety which she was unable to control. She has frequently sought assurance in the doubts bred in her mind by renewed presentment of the obsessing ideas ; thus at one time on waking in the morning she could not rid her thoughts of the idea that she might have masturbated during the night. She confessed to having no recollection of having done so and assured me she had quite given up the practice ; still she was obsessed with the idea that she might have done it "without knowing." She would feel compelled to lie in bed and argue with herself as to whether or no she had really done this, and if so, her hands being soiled and unclean how was she to get out of bed and without touching something, how could she wash her hands before getting out of bed, etc.? Under these circumstances it was necessary to reassure her that her fears were unfounded and that she might confidently get up. On another occasion she came to me in a sad dilemma concerning a box of clothing she had left at home ; she was unable to rid her mind of a doubt as to whether a piece of rubber tubing (douche) might or might not be in this box. She sought my advice as to whether, in case her fear was warranted, I thought all her clothes would be contaminated, and if so would it be sufficient to have them washed thoroughly or should she have them all destroyed ? She always washed herself scrupulously and continued doing so until the nurse told her to desist. She informed me that she preferred that the nurse should be there as a witness who could reassure her later on in the day that she really had thoroughly cleaned her hands. She continued for many months to have attacks of anxiety associated with these obsessive ideas and ruminations. It will be observed that the idea of masturbation or some associated idea was frequently present in her thoughts ; but this idea was less repressed in the later periods of her illness, principally, I think, on account of our free

discussions of her case, in which attempts were made to give her a deeper insight into the factors conditioning her trouble. She made considerable progress, and had much greater control over herself when she was transferred to another asylum.

The second case has many points of interest which may be compared with the foregoing one.

Elizabeth D—, aged 39 years, married, was first admitted to the asylum in June, 1907, suffering from depression of mind and an impulse to wash her hands.

Particulars of the early life and development of this case are scanty, and contain nothing of special interest. She is a moderately well-educated woman, and was formerly capable in household affairs. She was married at the age of twenty-three. In disposition she was reserved, retiring, and very timid in society. She suffered from erentophobia, and was described as being of a very nervous temperament. She was much disposed to trivial worries and anxiety, and was afraid of any conditions strange or unusual to her habitually quiet existence. The first year or two of marriage appear to have been uneventful. She was simple in her aims and wants and was fairly happy and contented. The first confinement was prolonged and difficult, and this experience caused her to wish to have no more children. From this time preventive measures were successfully employed and she was never again pregnant. The ensuing years showed the gradual development of morbid symptoms culminating in the neurosis from which she is now suffering. Her predisposition to worry became more noticeable, a state of disquietude gradually became habitual with her, and she suffered frequently from vague anxiety. Self-criticism and a feeling of incompetence and indecision accentuated a natural tendency to seek sympathy and affection, and to rely more than ever upon the guidance of her husband. Now the advent of these symptoms in the wife was followed by a change in the husband, in whom there developed a growing coldness of manner; gradually in the course of the following years the conjugal relationship became more and more strained; associated with this change there developed an increasing tendency to sexual indifference. In 1897, when she was twenty-nine years old, she nursed her husband through a serious illness, during which he seemed to turn against her, and she was constantly troubled by the idea that they were drifting apart. Five years later her husband was again ill, and she again nursed him under very trying circumstances, for he became more and more disagreeable, and at times it seemed to her that he could not bear her presence near him. One day subsequently

to these events she observed her child at play with another child who was suffering from ringworm; many years before this her baby had had this disease; recovery had taken place in due course, and at the time no undue importance was attached to the incident. Now, however, she displayed extreme anxiety fearing that infection might have again taken place, and long after there was any possibility of this having occurred she continued to have unreasoning fears, which she was unable to control. She persisted in taking every precaution she could think of to protect the child from further infection, and maintained a constant and anxious observation of her scalp and skin; actuated by the idea that infection might have already occurred she made use of every sanitary precaution against the possibility of conveying the disease or getting the house and clothing contaminated. The fear of infection constantly forced itself upon her, incapacitating her from her usual occupations, and compelling prolonged and profitless ruminations. This state of mind continued with remissions for the next few years, the attacks always returning with increasing severity, and leaving her more and more aboulie. In these crises of anxiety and doubt she sought relief in a prolonged washing of hands. This habit became more and more uncontrollable and developed into the impulsion which brought her to the asylum.

She is a woman of medium build and is well nourished. On admission there were chilblains on the hands, the skin of which was red, glazed, and exfoliating in patches. There were signs of a well-compensated mitral cardiac lesion, but she was otherwise in good health; the reflexes were normal and sensation unimpaired.

One maternal aunt was known to have been insane.

Her manner was quiet, and she appeared calm and self-possessed except for an expectant and slightly anxious expression. She replied willingly, the attention being well maintained and the reaction not delayed. She gave a good account of herself and her memory was unimpaired; orientation was normal. The prevailing affective tone was one of mild depression and anxiety. She spoke and reasoned intelligently and with self-control. She showed much insight into her condition and circumstances, and quite realised her position. She complained that she was unable to prevent herself from persistently washing her hands. She realised that it was something abnormal in herself which she desired to be cured of, and she recognised that she was in the asylum on account of this abnormality. She told me all the details of the ringworm and of her obsessive ideas and fears, but she made no mention of her relations with her husband.

There was a marked feeling of self-insufficiency. She informed me that she had always been nervous and timid, and that for many years she had felt strangely anxious, had lost all confidence in herself, and that she had been subject to fears and anxiety about her child, which quite incapacitated her from her usual occupation. After a week or so a rapid improvement set in, she felt herself again, and the impulsion entirely disappeared. She returned apparently quite willingly to her husband, and seemed to have entirely recovered.

In March, 1909, she was readmitted. It transpired that the return to her old environment had been associated with a recurrence of anxiety and unrest; gradually the same fear of infection took hold of her mind, and with it the impulsion returned. Although she was able to control these symptoms to a certain extent, she had been in an almost constant state of doubt and self-interrogation. The anxiety she had formerly experienced concerning her child now appeared in a more generalised form; thus, if she chanced to meet a child in the street, she was liable to begin arguing with herself as to the possibility of that child being infected with some disease, and in order to avoid a meeting she would turn back and reach home by a long detour and then subject herself to prolonged ablutions. On one occasion, seeing the baker approaching the house, she observed that he stopped and spoke to a child, she at once became very uneasy and alarmed, and refused to take in the bread which he brought. She was only reassured by her husband's promise that they would employ a different baker. At times her anxiety associated with this idea of contamination spread to the house generally, and on one occasion she cleaned everything with paraffin, including the inside of the piano, pouring this fluid about instead of using it upon a cloth, because, as she argued, the cloth might possibly contain some germ of infection. The idea of infection was at this time less defined, and not particularly associated with ringworm, but her child was always the special object of her concern. There was a strong feeling of personal contamination which compelled her to wash after touching any object.

When she returned to the asylum she was at once more self-possessed, and her mental state was very similar to that already described. She now for the first time confided to me that her husband had not been kind to her, that she was unhappy at home on this account, and that he was the cause of her relapse. She rapidly became well again, and in the following October was again discharged as recovered. She stayed awhile with her sister, and then returned to her husband. After a few weeks

she became unhappy and restless. She began her ruminations again, and was unable to sleep. The fear of a return of her trouble caused her to write to me for advice; she complained of a return of her feeling of anxiety and loss of self-confidence, and said that she relied entirely upon me, and would return to the asylum if I thought it best for her. After six weeks' absence she was again admitted. She was despondent and resigned, and was suffering from the same washing impulsion; there was, however, no dominant idea in her mind associated with the action, which now appeared more automatic. She seemed relieved to be back again. This attack was more persistent, and was marked by the same feelings of incompetence and the same want of self-confidence. She has always retained a perfectly sane judgment in the matter of her impulsion. She improved slowly, and is now almost free from her trouble, but for a long time there was always a feeling of apprehension when the question of her discharge was raised. She often showed anxiety and indecision in respect to her relations with her husband. It was now for the first time that she made a full confession of these relations in reference to which there is always evident in her mind the conflict between opposing trends: thus she would maintain that he had treated her shamefully, that he was the cause of all her trouble and that she would never live with him again, yet she never seemed to relinquish the hope that he would be unable to live without her. She continued to receive visits from him, though he often seemed unsympathetic and unkind to her, and when quite recently he became dangerously ill, she showed the greatest concern and anxiety to be with him and care for his wants.

There are certain features which are common to these two cases.

(1) General temperament: Both these patients were timid and reserved in disposition, they were subject to creutophobia, shrank from publicity, and showed a general want of self-reliance. They were self-critical and particularly scrupulous in the less important affairs of life. There was a ready tendency to become discouraged, and they were frequently subject to feelings of effort and of incapacity.

(2) The liability to states of anxiety.

(3) The tendency towards hesitations, doubts, self-examination, and endless questionings (ruminations).

(4) A resulting inability to arrive at a decision or action, particularly in matters which concerned themselves (abulia).

(5) Phobias, of infection, of contamination, of contact.

(6) Obsessions of personal uncleanness.

(7) Compulsive actions, *e. g.* constant washing of hands.

All these symptoms have been frequently described by various writers; formerly, however, they were regarded as belonging to a number of distinct diseases, *e. g.* "*folie du doute*," "obsessional insanity," "impulsive insanity," etc.

Now Janet, in his great work on '*Les Obsessions et la Psychasthénie*,' published in 1903, pointed out a common form of reaction underlying certain mental states; these included, besides those already mentioned, the mental "manias," various states of anxiety, phobias, and diverse forms of agitation and tics. These he collected together, and showed, in an exhaustive study, that they shared a common basis and that they could be interpreted by reference to a single theory. To this group he gave the name of "psychasthenia."

In this reaction he observed a disorder in the functioning of the mind presenting the same essential characters independently of the particular function involved; the function reacts in a manner which is not only exaggerated, but inefficient and beyond the proper control of the subject. There is no complete paralysis of the mental processes, but they are liable to be checked or insufficient; thus there is a failure in the attainment of certainty and of belief in thought, and in action the execution is incomplete. This failure is accentuated in the presence of others, or as the mere result of a subjective effort of attention; moreover, even when the functioning appears complete, there is a subjective feeling of incompleteness accompanied by feelings of incapacity, uneasiness and anxiety. When placed in circumstances demanding action or decision, the consciousness of this incapacity tends to promote crises of agitation and diffuse anxiety. The mind, incapable of complete action, thought or feeling, becomes conscious of having forced upon it doubts and questionings, and is liable to forced ruminations and reveries, or to a variety of forms of "manias," *e. g.* of precision, of counting, or of explanations, precautions, etc. In this state of mind the essential disorder appears to have reference to an absence of decision and of the power of resolution, to an absence of belief and of attention, and to an inability to realise an exact perception of the present moment. In order more readily to resume these various troubles in a single conception, Janet propounded the idea of a special function of mind, which he named "*La fonction du réel*" (1). On the quality of this function depends the individual's power of apprehending reality whether in perception or in action. "To understand a perception or an idea with a feeling that it is reality, this is to co-ordinate round that perception all our

tendencies, all our activities; it is the complete accomplishment of the attention" (2).

The loss of this function is that feature above all others which characterises the phenomena of psychasthenia. It is exemplified in the feelings of incompleteness of automatism and of being in a dream. The psychasthenic often complains that he is only half alive or that his soul is separated from his body; he experiences feelings of strangeness as if he were in another world; his environment seems changed and unreal. In the abstract in imagination and in affairs which have little importance or barely touch on reality he is able to act without difficulty; but when action becomes important, when the social environment becomes difficult, or when there is question of reacting on concrete reality, he fails.

Hence it comes about, then, that while in states of psychasthenia there is a deficiency in those phenomena of mind upon which depends the exact adaptation of the personality to the present situation, the power of attention, the faculty of belief, the feeling of reality, and the power of completely assimilating new perceptions—in short, the qualities of a mind of the highest level of efficiency—in these same states we find preserved or exaggerated those mental phenomena to which the personality attaches little interest or importance, phenomena of a simple kind exacting no complicated or new co-ordination of ideas, and no strain upon the attention, phenomena to which the mind is already well accustomed, and which have little bearing on reality or relation to an immediate and new set of circumstances. Now the functioning of the normal mind is subject to oscillations of its level of efficiency; it is influenced by fatigue, by sleep, and by emotions, it has a definite relation to age, experience, and education. These oscillations may be observed also in a number of diseased mental states, in which they undoubtedly play an important but subsidiary part. The psychasthenic mind, however, is essentially characterised by an instability of its level of efficiency, by its inability to maintain a high level, and by the readiness with which under various influences it tends to become rapidly lowered.

This lowering of the mental level (*abaissement du niveau mental*) Janet has explained by the conception of a variation in the mental tension (*la tension psychologique*). The degree of this tension is dependent on the number, richness, and complexity of the elements in consciousness, together with their unification and concentration in a new synthesis. The lowering of the mental tension, therefore, would render difficult or impossible the conscious realisation of those higher phenomena of mind connoted in

Janet's "*fonction du réel*," viz. the consciousness of personality and the feeling of freedom in voluntary action, the perception of reality, belief and certainty, and the faculty of realising satisfaction in the reaction of the present moment. The consciousness of this deficiency and mental void is expressed by the subject in all manner of feelings of incompleteness. The psychasthenic is always comparing his present incapacity with the best achievements of his previous experience; he possesses ideals of a perfection impossible to him; hence the feeling of insufficiency and the resulting abulia, ruminations, and self-criticism. From these are derived the various "manias" of precision, explanation, etc., and ultimately the obsessive ideas. "An obsession is the final result of the lowering of the mental level; it is a sort of interpretation which presents itself perpetually to the mind, so long as the fundamental disorder which underlies it persists" (3).

The obsessive ideas of psychasthenia are, as Janet has pointed out, always critical in nature and derogatory towards the actions and thoughts of the subject; they have, moreover, a particular reference to their persons, ideas, and actions, or to their bodies. He, therefore, regards them as endogenous in origin, and contrasts them with the exogenous fixed ideas of hysteria. A feeling of incompleteness always precedes or accompanies the psycholeptic crisis, and a vague anxiety drives the sufferer to seek some form of excitation. The reaction to this stimulus, usually some symbolic action, is passionately pursued, and brings with its accomplishment a certain amount of temporary relief. The impulsion thus set up tends to persist because the abulic mind is incapable of conceiving an alternative remedy; it continues so long as the feeling of anxiety remains. In a paper on "The Pathogenesis of some Impulsions" (4) Janet has emphasised these points, and shows how these excitations are satisfied by actions which are normally exciting to everybody; even the impulsion to inflict pain upon oneself (as in observation 5) can be traced to the need of courageously bearing pain. The central idea of the obsession is the expression of an explanation which the patient arrives at in the interpretation of his own mental state; it is his own theory of the transformation, of which he is painfully conscious in himself. Thus, Caroline M—, though she recognised her own scrupulously moral character, came, through feelings of anxiety, doubt, of suspicion and shame, to interpret the change in herself by an obsession of uncleanness and sin. In the psycholeptic crisis these ideas form the content of ruminations and are forced on a mind which constantly experiences a need for precision, for explanation, and for some symbolic

expression of its feelings of incompleteness and psychic insufficiency; they have, moreover, reference to actions and thoughts of a painful nature which the patient would not desire to accomplish; they constitute, in fact, a delirium of auto-accusation, and are developed in the mind of the subject as a confession of a state of impotence in which the process of thought cannot be carried to its logical conclusion, and which perpetuates a state of doubt regarding his actions and beliefs. The obsession is then regarded by Janet as a further manifestation of that lowering of the mental tension by which he has interpreted the phenomena of psychasthenia in general.

Amongst the associated causal factors concerned in the abnormal oscillations of the mental level we must again refer to the influence of states of fatigue and of bodily illness, but especially to the influence of emotions. These latter, as Janet has shown, are associated both with the rise and the fall of the mental tension, and he remarks that they are often both the occasion of and the feeling experienced in marked changes in the mental level. He holds the view that emotions, while they are frequently important associated factors, still, cannot be held to offer an adequate explanation of the phenomena. The psychasthenic often shows a tendency to a feeling of indifference; but this is not the indifference of apathy, it is an indifference which he constantly criticises and deplores, his great trouble in his incapacity to feel a real and complete emotion over anything.

To explain the phenomena which he has shown to depend on variations in the mental level and also his conception of a deficient mental tension, Janet has put forward his hypothesis of a failure in mental synthesis; this latter process he describes as "an operation which unites in one single and new composition the elements furnished at each moment of life by the senses and by the memory" (5). Further, he conceived the mind of these patients to be in a state of molecular disintegration, in which condition all the sensations, ideas and memories were assumed to be loosely bound together. It is instructive to turn for a moment to compare this conception with that suggested by Janet to explain the phenomena of hysteria; here he conceived the idea of a molar disintegration to account for the splitting and contraction of the field of consciousness. In this latter condition the ideas, memories, etc., are assumed to be compactly associated, but liable to be split off in lumps as it were. The dominance of certain associated systems of ideas would then lead, by exclusion of others, to the narrowing of the field of consciousness, but within this narrowed field the functioning of the mind may appear normal.

We have, then, in this far-reaching interpretation of Janet's, to the magnitude of which the limits of a short paper render it hopeless to do adequate justice, the practical conception of a form of reaction which is invaluable in its application to clinical phenomena as well as in the intelligent understanding of the problems they present. Both Caroline M— and Elizabeth D— are examples of this reaction; the former case belongs to the constitutional variety of psychasthenia; the latter should perhaps be regarded as an acquired form, the earlier history being inconclusive. The occurrence of obsession-impulsions in these cases is only in accordance with innumerable observations, particularly by Janet. Bianchi observes, "I have never seen a subject suffering from obsessions who was not uncertain and hesitating in most of the actions of his life" (6). As regards the ætiology of obsessions this writer holds that indispensable conditions are (1) an excessive emotivity, and (2) congenital or acquired weakness of the mental organism.

Störriing also lays stress on the importance of emotions, and particularly of anxiety. In the latter half of the nineteenth century there were two opposing theories to explain the origin of obsessions. There was the intellectual theory, supported by Griesinger, Westphal, Hack Tuke, and Magnan amongst others; with certain individual modifications, it advanced the conception that the essential factor was a disorder of the intellect, and that all other symptoms were subsidiary. On the other hand, there was the theory advanced by Morel, and supported by Legrand du Saulle, Wernicke, Féré, and by Pitres and Regis, which held that the intellectual phenomena were secondary to a disorder and disturbance in the affective life. Until recent times this latter theory was generally accepted by the majority of observers. Janet, however, pointed out that neither of these theories offered an adequate explanation of the phenomena. He sought a wider interpretation, and regarded the emotional factor as also subsidiary. Janet based his conclusions on innumerable observations on the evolution of morbid states of mind, which enabled him to place these syndromes in large groups exhibiting similar reactions. It is noteworthy that he constantly observed the modification or exaggeration of normal psychic processes underlying the phenomena of disease. He regards the obsession as the reproduction of a former event or idea which at the moment of its appearance was not the cause of any trouble, but which becomes pathological at the instance of a new emotion.

As regards the form of the impulsion, Störriing (7) has insisted on the importance of "strain-sensations" or muscular hallucinations as playing

an essential part in the development of the action. In reference to this it may be noted that Janet observes that the subjects of impulsions have representative images in their mind which harmonise with the execution of the desired act, and he has remarked on the exhibition of more or less involuntary little muscular movements which are like the beginnings of these acts; hence the patient frequently says he feels urged to perform the action.

Although Janet's interpretation can be applied to explain the evolution of the two cases of obsession-impulsion described above, nevertheless it fails to take account of certain points which appear fundamentally important to a more complete understanding of the morbid factors at work. The elucidation of these points we owe to the work of Prof. Freud.

The latter interpreted the phenomena of the psycho-neuroses, firstly by his conception of the unconscious mind, and secondly, by constructing a conceptual mechanism designed to explain the morbid phenomena observed in these neuroses. He justified his theories by demonstrating that they satisfactorily account for the phenomena, and this he has been able to prove by his method of psycho-analysis and by the success of his psycho-therapy. For the present purpose only a brief reference is made to certain essential points of Freud's theory; a more detailed explanation is beyond the limits of this paper, and the reader is referred to several articles on the subject recently published by Bernard Hart (8) and Ernest Jones (9).

Inquiry into the intimate experiences and history of patients frequently brings to light the existence of a mental conflict between, on the one hand, the personality, and, on the other, a complex* of a painful nature and with which it is out of harmony. Under these circumstances the mind endeavours to rid itself of the complex and to forget its existence. The process by which this is effected is known as "repression"; "the effect of repression," to quote a recent paper by Bernard Hart (8), "is to prevent the complex exerting its normal action upon the flow of consciousness; that is to say, the complex can no longer cause its constituent ideas to emerge without resistance into consciousness, and it can no longer cause the flow of thought and action to proceed in the direction of its own conative trend. Repression means, therefore, that a certain resistance is opposed to the

* The word "complex" first used by Jung has now come into general use. A complex presents these aspects: (1) Intellectual elements; (2) the affective tone appertaining to these elements, (3) certain definite conative tendencies (Hart) (8). In a recent paper by E. Jones a complex is held "to indicate the whole group of mental processes relating to a given set of experiences that have become invested with a strong feeling tone, usually of a painful nature" (10).

complex which prevents the latter affecting consciousness in its normal manner." To this resistance Freud has given the name of "censure" (*Zensur*).

"In spite of repression and the censure, however, the complex preserves an autonomous existence" in the unconscious (Freud), "and continues to influence the flow of phenomenal consciousness, but the influence is now distorted and indirect."

By this mechanism Freud claims to explain many of the obsessions; an obsession is an idea in consciousness that has become overweighted, due to the fact that there has become attached to it the affect originally belonging to a repressed complex. The obsessive idea is frequently, though not necessarily, the opposite of the one repressed, and often stands in a symbolic relationship to it.

In the case of Caroline M— there is unquestionable evidence of a conflict between her naturally scrupulous and moral personality and the ideas associated with a morally objectionable and repulsive habit. She succeeded in overcoming this habit, but the complex remained in her mind. An examination of the clinical evidence justifies the assumption that the components of this complex would for the main part consist of—(1) ideas associated with masturbation; (2) the desire to obtain gratification by resorting to this practice. Opposed to this would be the conative trend of the personality towards a moral life, depending on her early education and environment. Between these opposing complexes a conflict must inevitably arise, and this conflict would express itself in feelings of remorse, disgust, self-reproach, and anxiety. In order to avoid the conflict the process of "repression" would come into play. That this masturbation complex had been more or less successfully repressed there is, I think, sufficient evidence in the patient's attitude towards her onanism when I first examined her. She voluntarily came to the asylum because she realised her morbid state and sought relief. Her complaint was her impulsion to wash, and the uncontrollable idea that she was contaminated and wicked. She did not admit or recognise any causal relationship between these symptoms and the onanism, which when questioned she sadly confessed to as a regrettable incident in her life. She, however, obviously did not attach any importance to this episode, which held no disproportionate place in her conscious thought. In this ignoring of the real significance of the masturbation we have evidence of the partial repression of this complex. In the second place there is evidence of the exaggerated conative trend of the personality which appeared in an increased tendency to scrupulousness in her manner

of life, especially in the direction of an excessive personal cleanliness and in the desire to be regarded as scrupulously clean and proper in her person. The incident of the stained and soiled linen presented an idea opposed to this trend and unconsciously stimulated the repressed complex; hence feelings of anxiety and suspicion arose in her mind respecting the opinion of her fellows. Thirdly, we have the complex expressing itself symbolically in the idea of uncleanness and leading to the symbolical action of washing the hands.

The personality would not tolerate the avowal of the real occasion for its feeling of uncleanness; the repressed complex could only elude the censure by an indirect and distorted expression not essentially repugnant to the mind. But owing to the fact that the irritant cause, *i. e.* the offending complex, remains repressed and undispersed, the morbid affects thus symbolically expressed tend to persist, and the obsessive idea and impulsion continue to force themselves on the mind in a manner which is subjectively recognised as entirely unbalanced by facts and as wholly irrational.

The exercise of the censure constantly detracts from the available mental energy and thus renders the mind abulic.

By this interpretation of the mechanism of obsessions Freud has rendered intelligible the content of certain clinical phenomena which frequently appear wholly haphazard and unaccountable. Although he differs from the interpretation given by Janet, the recognition of the intrinsic meaning of psychasthenia, *i. e.* the grouping of a mass of clinical material presenting a certain form of reaction, broadens the basis of our knowledge of the psycho-neuroses, and paves the way to a realisation of the significance of Freud's theories.

Briefly to summarise the principal factors in the case of Caroline M—we have—

- (1) A constitutional predisposition—a certain type of reaction characterised by psychic self-insufficiency, tendencies to abulia, etc., symptoms frequently observed as here, in association with imperative ideas and actions, and which we may conveniently recognise under the name "psychasthenia."
- (2) The incidence of a painful experience affecting the sexual life.
- (3) The conflict between mutually incompatible feelings and conative trends and the barring from consciousness of the offending complex.
- (4) The inevitable tendency of the repressed complex to influence and disorganise the mental life of its host.
- (5) The evolution, resulting from these forces, of a psycho-neurosis.

Turning next to the case of Elizabeth D—, the problems presented are considerably more complicated and scarcely permit of more than a simple review of the facts. The application of the method of psycho-analysis to this case would probably reveal many factors elucidating the development of the clinical symptoms. Still, recognising this deficiency, the case appears to have considerable interest, both in comparison with the other comparatively simple case described above and also in reference to these questions of ætiology and of interpretation. The recognition of Freud's mechanism enables us to gain a far deeper insight into the problems presented in our daily clinical observations, both in respect of a more scientific classification of material and also in reference to the questions of prognosis and treatment. This recognition obtains especially in the practice which deals with large numbers of cases, where the more complete methods of analysis are impracticable.

In this second case an examination of the principal factors reveals a closely similar mechanism to that in operation in Caroline M—. This woman was naturally dependent, and felt the need of domination, sympathy, and affection. These she found in her husband, and married life started favourably. Then came an important factor—the interference with the normal conjugal relationship and the practice of prevention, which in this case took the form known as “coitus interruptus.” Freud (11) has called attention to the evil effect of a frustration of the normal somatic and psychic satisfaction, and has observed the frequent incidence of this form of sexual trauma in the histories of patients suffering from anxiety neuroses. He goes so far as to hold the view that in this factor is to be found the principal cause of the neurosis. I will only record the observation that the abnormal state of anxiety in this case bears a chronological relationship to the practice which was carried on for some years, and that her morbid emotivity was followed by the development of vague fears relative to conjugal estrangement, to the health of the child, and to the possibility of infection from ringworm.

Pari passu there was the development of a real sexual indifference, chiefly on the husband's side. The patient was constantly distressed by the idea that her husband cared less for her, and came to realise the full import of this fact in the repulsion he showed during his illness. Thus the whole trend of events evolved in her mind certain painful complexes at conflict with all her natural tendencies.

The ideas associated with her husband's indifference and unkindness towards her were clothed with feelings of a painful nature, of regret, self-

reproach, and anxiety for the future, and the conative trend of this complex tended in the direction of resentment and antagonism towards him, a feeling that has frequently shown itself since, often in association with contrasting feelings showing her real affection (*e. g.* as in his latest illness). The very nature of this complex at conflict with the personality (her affection for her husband, her desire to look after and care for him, her dependence on him and the idea of her home, and all that this meant to her) necessitated concealment in the social environment where she had no intimate friends and only unsympathetic relatives. The offending complex was too painful to be suffered to occupy her thoughts and was therefore persistently ignored and repressed. In this connection it may be recalled that for a long while after she came under my care she concealed these facts from me, although freely giving me her confidence in other matters.

Her natural conative trend showed itself in her efforts to care for and nurse her husband, in face of his repulsion of her—in persistent tendencies to actions in justification of her desires, and when checked in this direction she showed an exaggerated development of maternal affection. The conflicts in this patient's mind are certainly extensive and complicated, and there is evidence of other complexes, *e. g.* such emotional disturbances as may be assumed to be associated with sexual frustration and the interference with sexual and maternal instincts, which could not be brought to light by the ordinary method of examination. An attempt is only made here to demonstrate the fact of the occurrence of conflicting states of mind and of the repression of painful ideas.

In conclusion, we may, therefore, again emphasise the practical significance of the recognition of Freud's mechanism in the interpretation of the evolution of these abnormal mental states, the ætiology of which may, in this way, be found in a study of the whole development of the personality and in the vicious influence exerted by the social environment upon the normal functioning of the mind.

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A Review of the Recent Literature in England and America on Clinical Psychology and Psycho-Pathology.*

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I. INTRODUCTION.

THERE have been four distinct movements in clinical psychology and psycho-pathology in Anglo-Saxon countries. The two that originated in England are practically dead so far as further progress is concerned; the American two are at the height of their vigour. At the head of these movements stand the names of Braid, F. W. H. Meyers, Morton Prince, and Adolf Meyer respectively. Associated with the first of these, Braid, the names of his predecessors Elliotson and Esdaile should especially be mentioned; with the second those of Gurney, Podmore, William James, and Hyslop; with the third Boris Sidis, Putnam, Coriat, Courtney, Linenthal, and Taylor; and with the fourth August Hoch and Macfie Campbell.

To the first of these movements, which may be dated 1840, we directly owe most of our modern knowledge of hypnotism. Braid's work was the inspiration for Azam, Broca and Velpeau, and to some extent indirectly for Liébault, from whom the Nancy and practically all other present-day European schools of hypnotism have sprung. Little, however, has been added to Braid's work. Hypnotism is still looked askance at by the medical profession in England, and even more so in America, though there are many physicians in the former country, notably Milne Bramwell, Lloyd Tuckey, Woods, and Kingsbury, and some in the latter, including Quackenbos and others, who devote themselves to the practice of it.

The second movement, which flourished most in the eighties, first in England and then in America, was productive of a mass of valuable experimental work on post-hypnotic suggestion, hallucinations, automatic writing, crystal-vision, etc. This is practically all published in the 'Proceedings of

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the Societies for Psychical Research.' From the first, however, much interest was manifested in such subjects as clairvoyance, telepathy, table-rapping, etc., and of late years the spiritistic aspects have dominated all others. The pronounced tendency of the members to spiritism did a great deal to discredit their work on other subjects, and is one of many causes why clinical and practical psychology is still coldly received in England.

The third movement was initiated by Morton Prince about twenty years ago, but most of the published work is less than half-a-dozen years old, and it is only within this time that he has achieved any considerable following. Though it has many independent features, it owes much of its inspiration on the one hand to the experimental and non-spiritistic work of the second movement mentioned above, and on the other to the investigations of the Paris school, particularly those of Pierre Janet.

The fourth movement is of still more recent date, and traces more direct connections with the continent, particularly to the Freud school. It is chiefly concerned with the psycho-pathological problems of psychiatry.

The present review refers chiefly to the publications of the past three years. A great number of articles, frequently of no value whatever, have appeared in this time, and in the list given above references are given to only about a tenth of the publications; it is hoped that the list includes all the best work on the subject. Many excellent articles by foreign writers, notably by Bechterew, Claparède, Janet, Jung, Pick, Sollier, and Soukhanoff, have been published in Anglo-Saxon journals in this period, but these are not included as they do not originate in any Anglo-Saxon school. Works on the subjects of hypnotism, sexology, religious psychology and social psychology are also excluded, so as to economise space. Much of the best work done anywhere on the latter two subjects has been American; a review by Pratt of the recent American work in religious psychology, in the '*Zeitschrift für Religionspsychologie*,' 1909, Bd. iii, H. 3, may be referred to. The leading Anglo-Saxon writer on sexology is Havelock Ellis, whose works are better known in Germany than elsewhere.

A word may be said as to the attitude towards clinical psychology prevalent in Anglo-Saxon scientific circles. This is quite different in England and America. In the former country the subject is viewed with a cold antipathy, and, so far as the present writer is aware, no scientific investigation whatever is being carried out on it; less than a tenth of the articles here referred to were published in English journals. In America,

on the other hand, there is a widespread cordiality towards the subject, though the value of this is largely counter-balanced by the superficial and uncritical views that, except in a comparatively small circle, generally prevail. Readiness to accept a psychogenetic origin of certain maladies is much more widespread in the American medical profession than in the English, and there is also in that country a very general interest taken in the problems by the laity, as is evidenced by the popularity of such books as Addington Bruce's "The Riddle of Personality," Hudson's "Psychic Phenomena," and Waldstein's "The Subconscious Self," etc.

Those who propose personally investigating any of the writings here referred to should be explicitly reminded that, as the account of them given in this review is based on the present writer's individual judgment, it is not likely to be quite impartial, though every attempt will be made so far as possible to make it so. The descriptions will further necessarily be incomplete and condensed, so that the danger of distorting the authors' views is especially hard always to avoid.

II. CASUISTIC, SYMPTOMATOLOGY, DIAGNOSIS AND TREATMENT.

In the symptomatology of *hysteria* valuable contributions have been made on the subject of blindness and other visual abnormalities by Baird (5), Diller (40), Gradle (59), Onuf (114), and Parker (116), on that of hysterical affections of the ear by Holmes (70) and McBride (96), and cases have been recorded of hysterical mutism by Hudson-Makuen (72), J. K. Mitchell (109), and Oettinger (113), and of aphasia by Le Kerr (93). It is held that hemianopsia never occurs in hysteria, a view also subscribed to by Mills (106). Studies of Ganser's Syndrome have been published by Diller and Wright (41), Frost (54), and Ruggles (143); the first named (42) and Woodman (191) have also contributed useful clinical discussions on hysterical insanity. It is generally thought that Ganser's Syndrome is not pathognomonic of hysteria, and that hysteria is comparatively rarely found in asylum cases. Detailed reviews on the subject of hysteria in children, with many illustrative cases, have been published by Hecht (63) and Thomas (166); it is dealt with from a purely clinical point of view. Hoover's (71) sign of hysterical paraplegia consists in the absence of the normal downward pressure of the heel when the patient raises from the bed the opposite limb. The present writer has published (77) a case of hysteria showing at four different stages in its evolution true tactile aphasia (in Claparède's sense), asymboly, *Tastlähmung*, and anæsthesia. He has also shown (81) that the current belief that hysterical hemiplegia

affects by preference the left side is founded solely on Briquet's opinion; in the cases published since 1880 the two sides are affected with equal frequency. In two further papers (78, '80) it is pointed out that allochiria is a pathognomonic symptom of hysteria; in the past it has been confounded with other troubles that may occur in organic disease. Dyschiria is an affection of sidedness, of which there are three forms; (1) achiria, in which the patient has no knowledge of the side of a stimulus; (2) allochiria, in which he refers it to the exactly corresponding point on the opposite side; and (3) synchiria, in which he refers it to both sides.

Deaver (36) and Williams (182) point out the importance of the mental factors in cases of *gastric neurosis*, and Cannon (16) deals with the same subject from the physiologist's point of view, relating the work of Pavlov and others on psychic influences in relation to gastric secretion.

Weir Mitchell (111) has published a case under the title "Motor Ataxy," and Scripture (152) one under the title "Penmanship Stuttering," which are evidently instances of *Angsthysterie*.

Janet's conception of *psychasthenia* has a great vogue in America, and the nosological status of the condition is generally accepted. Orthodox expositions of the subject have been given by Blumer (7), Collins (22), Courtney (31) and Donley (49). Of these Courtney's description is the fullest and most precise. Donley (43, 45) has published some cases of what Prince in 1891 described under the term "association-neurosis." By this is meant a syndrome, which may occur in various maladies, where the symptom (*e.g.* fear) is reproduced whenever the patient lives through an experience that is associated with the occasion on which the symptom first occurred. For instance, a patient who has once been frightened in a churchyard may experience fright whenever he meets anything associated with a church. The patient is usually relieved when he fully recalls and talks over the initial experience.

A meeting of the Neurological Section of the Royal Society of Medicine, London, on January 30th, 1908, at which Buzzard, Collier, Guthrie, Harris, Head and Ormerod spoke, was devoted to a discussion of *tic*. It followed the lines laid down by Cruchet, Meige and Feindel, and nothing new was brought out. Prince (125) has described a severe case of multiple *tic*, and expresses the view that the symptom is the manifestation of a dissociated automatism, due to the functioning of some subconscious mental process; the nature of this he could not determine.

Spiller (162) has an interesting article on the subject of *psychasthenic attacks*, of the type described especially by Oppenheim, and discusses the

diagnosis between them and narcoleptic attacks. In relation to this the present writer described a case (79) in which it was possible, by studying the subconscious memories related to the attack, to establish the diagnosis of hysteria; he contrasts the "massive" disaggregation of hysteria with the "molecular" disaggregation of psychasthenia. Putnam and Waterman (139) have also discussed the differential diagnosis between epileptic and hysterical attacks from a psychological point of view, and Camp (16), Hetch (64) and Taylor (163) have described other conditions of chronic narcolepsy. Coriat (25, 27) has been able to trace a relation between nocturnal paralysis (Weir Mitchell's syndrome), and repressed unconscious memories of painful experiences; he has described five cases of it, and advances good reasons for considering it a psychical manifestation, a "recurrent mental state."

Great interest was aroused in America in the subject of *multiple personality* by Prince's study of a case of this nature published in great detail in 1906 (126). It is certainly the best observed case of the kind that has been recorded, and is so well known that description of it here is not necessary. The book is purely descriptive in character, and is to be followed in 1910 by another volume in which the theoretical aspects of the subject will be dealt with. In a book that will presently be again referred to (154), Sidis published a case of double personality, and a number of like cases have since been recorded by Angell (3), Coriat (26), Dewey (39), Fox (53), Gaver (56), Gordon (57), Hyslop (73), and others. Hyslop's case showed a subconscious fabrication of Martian language similar to that invented by Middle. Hélène Smith, and probably founded on the knowledge of Flournoy's book. Studies on cases of ambulatory automatism have been published by Courtney (30), Lloyd (95) and Patrick (117); in the first mentioned article Courtney discusses the differential diagnosis between the various maladies in which this condition may arise.

The number of articles published on *psychotherapy* is very great, and the quality of many of them is decidedly poor. Practically all the European schools are represented in America. Thus Barker (6) advocates Déjérine's method of isolation, etc., Jelliffe (75, 76) advocates Dubois' "persuasion" method, Williams (176, 187, etc.) that of Babinski, etc. Prince and Coriat (132) hold that there is no distinction between persuasion and suggestion. They rely in treatment especially on tracing back as far as possible the origin of the symptom, particularly in hypnosis, on divesting it of its unpleasant associations (Janet's device), and substituting a fresh

group of pleasant associations. Hypnotism is, in general, not regarded with favour in America. Putnam (134, 135) advocates what he terms the "side-tracking" method, by means of which the patient's interest for healthy and useful mental pursuits is strongly aroused. He has inaugurated an interesting "Social Service" department in the Massachusetts General Hospital, so that patients may as far as possible be brought into a healthier and more stimulating environment. Emphasis is laid on the relation of psychotherapeutic treatment to the "social consciousness" by Putnam (137), Schwab (149) and others. Another and more original psychotherapeutic method is that devised by Sidis (159), and termed by him "Hypnoidization"; it has been extensively employed by Donley (47) and others. It will be discussed in the next section in connection with Sidis' other work. Münsterberg (112) has published a very interesting and useful book of a general character, but does not discuss individual methods in detail. On May 6th, 1909, the American Therapeutic Society held a symposium on psychotherapy. The papers read there have been published in book form under the title of 'Psychotherapeutics'; this includes, besides the articles above numbered 49, 84, 131, 159, 165, 172, one by Gerrish on "The Therapeutic Value of Hypnotic Suggestion," and one by Putnam on "The Relation of Character Formation to Psychotherapy."

The Emmanuel and other religious movements of psychotherapy have evoked a great deal of discussion in medical circles; their medical encroachments have been energetically opposed by Collins (23), Farrar (52), and Witmer (190). The relation between religious and medical efforts in this direction has been defined by Putman (138) and others. In this connection an interesting essay may be mentioned by Waddle (170) on miracles of healing.

Just now it is fashionable in America for patients to publish autobiographies describing their illnesses in great detail; such are: "My Life as a Dissociated Personality" by B. C. A., 'Journ. of Abn. Psychol.', October and December, 1908, 'The Maniac: A realistic Study of Madness from the Maniac's Point of View,' 1909, 'The Autobiography of a Neurasthene' (really a case of hebephrenia), by Margaret Cleaves, M.D., 1909, "The Mind that Found Itself," by Clifford Beers, 1908. It need hardly be said that most of such writings are of little scientific interest, as the essential points are never mentioned. Beer's book has been of considerable public service in drawing attention to a number of asylum abuses.

III. GENERAL PSYCHO-PATHOLOGY.

We may begin with some of the work of Morton Prince, who is unquestionably the leading Anglo-Saxon on "abnormal psychology." His first book, 'Nature of Mind and Human Automatism,' published in 1885, was devoted to developing a panpsychic theory. He has retained his interest for similar problems, and his latest work (130) is mainly concerned with the relation of conscious to subconscious mentation, and of both to unconscious cerebration. As was mentioned above, he has made a very great number of interesting observations on cases of multiple personality, and it is chiefly in the light of such cases that he formulates his conclusions on subconscious processes. For the study of them he makes use of direct observation, hypnosis, automatic writing, crystal gazing, and various specially devised and experimental tests.

Prince's work on the *subconscious* may be considered in conjunction with that of other writers; his views are developed especially in a series of articles on the unconscious (130), and in a review of a symposium on the subconscious published in the 'Journ. of Abn. Psychol.,' April and June, 1907. In the preface to this symposium he defines the six main connotations in which the term subconscious has at different times been employed: (1) the marginal region of diminished attention which at any given moment is outside the focus of consciousness; (2) active dissociated ideas of which the subject is quite unaware; (3) synthetised, self-conscious states, dissociated from the main consciousness, and forming a considerable part of every normal and abnormal mind; (4) all potential memories, including both the active dissociated states mentioned in the second definition and all past conscious experiences, which are now inactive, and which may or may not be capable of revival at a given moment; (5) a "subliminal" reservoir comprising the main consciousness, out of which the personal consciousness flows as a subordinate stream; (6) unconscious cerebration. The fourth definition is that adopted by Sidis, the fifth that adopted by F. W. H. Meyers. In the present symposium Münsterberg calls the third, second and sixth definitions given above the layman's, the physician's and the psychologist's respectively; he supports the last-named, and maintains that all the facts invoked in favour of the conception of the subconscious are adequately and more simply to be interpreted on the physiological hypothesis. Ribot, in a short contribution, also inclines to the same view. Jastrow, both in this symposium and in a book (74)

specially devoted to the subject, seems to maintain a similar position, but owing to the obscurity of the language in which it is couched the present writer is unable to understand and thus to present his point of view. Janet restricts the term subconscious to the second connotation given above, and regards all disaggregation as abnormal. Prince sharply divides the phenomena usually called subconscious, for instance as the term is used by Sidis, and also those included in Freud's *Unbewusste*, into two fundamentally different groups, which he terms co-conscious and unconscious respectively. Co-conscious ideas are synonymous with Janet's *subconscient*, and are mental states dissociated from the main personality. The subject is often not aware of their presence, but sometimes is, as in the case of an obsession. Thus for Prince not lack of awareness is the true criterion of co-consciousness, but independence and automatic activity that cannot be controlled by the subject. Further, "consciousness may be so rudimentary that it contains nothing of awareness, of self, of intelligence, or of volition." He stoutly maintains, as against Münsterberg and Ribot, the psychical nature of these states, and supports this view by a series of most convincing arguments and ingenious experiments (129, 130, 133, and 'Journ. of Abn. Psychol.,' June, 1907). Unconscious processes on the other hand, are not psychical, but physiological. They are divided into sub-groups: (a) cerebral neural organisations and residua the functioning of which is manifested as consciousness; (b) spinal and ganglionic organisations and residua the functioning of which is manifested as physiological memories; there is however no sharp line to be drawn between these two. "Purely physiological processes may manifest themselves in acts of quite as intelligent a character as those exhibited by the conscious processes." Prince uses the term dormant consciousness to denote those physiological residua into which mental complexes pass when out of mind. "It is the unconscious, rather than the conscious, which is the important factor in personality and intelligence. The unconscious is the storehouse of our minds. The secret of our moods, our impulses, our intelligence, our acquisitions, our attitudes, our judgments, our capacities, is to be found in its conserved dispositions." These dormant memories may or may not be capable of voluntary recall; if not they may be capable of being recalled through the use of special technique (hypnotism, etc.). Again "dissociated dormant complexes that cannot by any means be awakened to a conscious memory may be aroused into activity as an independent co-conscious idea," "If the term *Unbewusste* is not restricted to co-conscious great confusion arises, and this very

confusion underlies the psycho-pathology of the Freud and Zurich schools." Prince warmly criticises Freud and Jung for being so "vague" about the difference between co-conscious and unconscious functioning: "Freud's theories are severely impaired by defects which would seem to have followed from his entire disregard or unfamiliarity with the methods and results of experimental psychology. If we are to establish sound principles underlying the mechanism of the mind, we must correlate the findings of all methods of research, experimental as well as clinical, and give due consideration to the results obtained by all competent investigators." His criticisms, in which he chiefly cites Jung, are not easy to follow, especially as he uses the term "complex" in a special and personal sense. The main criticism seems to be of Freud's conception of the functioning of the *Unbewusste*. Prince holds that Freud's facts may be explained in two ways without invoking this conception. On the one hand the stimulation of an unconscious complex (*e.g.*, in the word association test) may cause this to function as a co-conscious idea, in which case there is no unconscious and purely physiological cerebration, as he thinks Freud believes in. On the other hand a given complex that is being stimulated may have become split, so that the emotion has become secondarily attached to an indifferent idea. Thus a given test-word may evoke a painful emotion, not because the underlying complex is stimulated to functional activity, but because the emotion originally connected with the complex has become secondarily attached to an associated idea, which is represented by the test-word. In this case the underlying complex does not function, and is not concerned in the manifestation of the emotion, though it may historically have been concerned with the genesis of it.

Prince seems to accept as proven the activity of co-conscious ideas only when these can be experimentally demonstrated, and he has published a large number of instances in which he has done this by means of automatic writing, crystal gazing, and other methods. The principles of dissociation and of automatism of dissociated ideas are the two on which he lays most stress in psycho-pathology (124). He has, however, not elucidated any of the actual mechanisms by means of which these dissociated ideas function. On the subject of multiple personality he has recently written, besides the book referred to above (126), a very interesting paper (128) comparing ordinary hysteria with this condition. He regards all cases of hysteria as a *forme fruste* of multiple personality, and insists that in neither case is any amnesia necessarily present. The paper contains a tabulated summary of twenty of the best recorded cases of multiple

personality, and it is pointed out that in some of these (*e. g.* Félicité X) the new condition that appeared was wrongly thought to signify the development of a new and superior personality, whereas really it signified the synthesis of two halves of the personality, one of which had previously been in abeyance from childhood.

Sidis' first book, 'The Psychology of Suggestion' 1897, was also concerned with the question of the subconscious, which he defines in the fourth sense given above; it contains many original and interesting ideas, which however cannot here be considered. His second book, 'Psycho-pathological Researches in Mental Dissociation,' 1902, is an account of experimental observations on amnesias, anæsthesias, "recurrent mental states," disaggregation, motor automatisms, etc.; it is shown that the attacks in psychic epilepsy are the manifestation of dissociated mental states. Sidis has recently contributed a series of extensive articles on the subjects of perception and *hallucination*. In one of these (157) he maintains that ideational and perceptual processes are fundamentally different in their nature; a percept differs from an image in having intensity, in bearing the mark of externality, in being immediate experience, and in that recall of it is independent of the will. He divides the elements of a percept into two, primary and secondary sensory elements; the former arise from direct stimulation of a sense organ from the outside, the latter from irradiation of this physiological process on to other sense structures. Thus when one looks at a table one *sees* the colour, form, etc. (primary sensory elements), but one also *sees* the hardness, weight, etc. (secondary sensory elements). In this article and in a previous one (153) he maintains that hallucinations are purely sensory in nature and differ from normal percepts in that the primary sensory elements are dissociated, and so are not apprehended in consciousness, while the secondary sensory elements constitute the hallucination; all hallucinations are due to peripheral stimuli acting on a subject with a tendency to mental dissociation. The "hallucinations" suggested during hypnosis, on the other hand, are, according to Sidis (155), totally different from true hallucinations; they are not percepts but images, and should more correctly be called delusions. In another series of articles (158) Sidis deals with the subject of sleep. Dividing the explanations into physiological, pathological, histological, psychological, and biological he strongly supports the last named, and agrees with Claparède in regarding sleep as an active protective instinct. He relates a number of experiments carried out on lower animals (frogs, guinea-pigs and dogs) and infants by means of monotonous

stimulation, limitation of movement and inhibition of external impressions. He sees in a certain half-waking state, which he terms "hypnoidal," the primordial biological state out of which both sleep, and hypnosis have later developed. The hypnoidal state, which does not seem to differ from Brémond's *état de fascination* and Forel's *Hypotaxie*, is intermediate between the waking state on the one hand and sleep and hypnosis on the other. It is induced by the application of monotonous stimulation (*e. g.* the sound of a metronome) while the subject is in a condition of relaxation, and is an unstable, fleeting condition. In the hypnoidal state it is determined whether sleep or hypnosis will ensue. Sleep differs from hypnosis essentially in that the psycho-motor thresholds are higher than in the normal (*i. e.* psycho-motor activities are less excitable), whereas in hypnosis they are lower; in the hypnoidal state a redistribution of thresholds occurs.

Sidis' recent work in *psycho-pathology* is presented in his third book (154), and in a series of papers entitled "Studies in Psycho-pathology" (156). He uses very special language in the exposition of this, such as "fading moments," "recurrent psychomotor states," "moment consciousness," and refers to various different states as hypnoid, hypnoidic, hypnoidal, hypnagogic, hypnoleptic, hypnapagogic, hypnonergic, etc. The book contains a valuable collection of instances of multiple personality, and includes, amongst others personally observed, an account of the celebrated Hanna case. This was a patient with profound and total retrograde amnesia, even for the meaning of everyday objects such as articles of diet and clothing, and Sidis gives an interesting account of the order in which the resurrected memories flashed back and gradually became synthetised. To this he adds a number of considerations on the theoretical aspects of the condition and of the various abnormal mental states. Sidis has had a great experience in the study of psychical amnesias, anæsthesias, synthesesias, and other types of dissociation. Dissociated mental activities sum up for him a great part of psycho-pathology, but in considering the genesis of them he rests content with such factors as psychic trauma, emotion, impression, etc.; the wish side of the phenomena is hardly considered. Similarly he has not brought out any of the mechanisms by which these dissociated activities manifest themselves. Recurrent motor states is the name he gives to the symptoms of the *Zwangsneurose* and psychic epilepsy; these he traces to the manifestations of subconscious activities (he uses "subconscious" in about the same sense as Freud's *Unbewusste*.)

Sidis attaches great therapeutic importance to the use of the hypnoidal state (154,156,159). In this state the patient obtains access to subconscious memories that are otherwise difficult to reach, but Sidis maintains that the mere making conscious of these is in itself inefficacious. The action of the hypnoidal state lies rather in the release it permits of stores of potential subconscious energy; this released energy brings about a synthesis of the previously dissociated mental states that now come to the surface.

In an article written in common with Prince and Linenthal (161) Sidis deals with the *pathology of hysteria* in the light of a given case. It is shown, by Janet's methods, that the hysteric anæsthesia is really only a psychical anæsthesia, and that subconsciously hyperæsthesia is present. Hemi-epileptiform attacks were in hypnosis traced to their first occurrence on the occasion of a severe fright, though no explanation is given as to why this particular symptom should have followed. When the patient was able to remember that in the attacks he was again living through the fright experience they ceased. It is concluded that hysteric symptoms are the manifestation of the automatic activity of a subconscious group of ideas, the dissociation having in this case been brought about by the fright. "Dissociation and automatism are the two fundamental processes in hysteria."

Coriat (24, 28) relates several cases in which he has been able, by experimental methods, to bring back the memories lost in alcoholic amnesia and other conditions; in discussing the mechanism of amnesia he does not consider the process of *Verdrängung*. Verrall (169) has given an excellent account of automatic writing as developed in herself. In a number of papers (80, 86, 89) the present writer discusses the pathology of dyschiria in general, and allochiria in particular. In the common form of hysteric anæsthesia only the incoming sensations are dissociated; in the rarer form (depersonalisation) there is in addition an amnesia for the past memories of the part of the body in question. If the latter are dissociated and not the former, a rare occurrence which the author calls "paradoxical type of cleavage," then dyschiria results, at first in its simplest form, achiria. Sensations evoked by stimulation of such a part have six characteristic features, which the author groups under the term "phrictopathic" (83). Allochiria is a secondary result, and a teleological hypothesis is advanced explaining its occurrence as an erroneous association that subserves the function of enabling the lost bodily memories once more to be apprehended in consciousness. A detailed study of two cases is related (86), which is held to disprove Janet's "image hypothesis" of allochiria.

Several writers have discussed the pathology of hysteria. Woodman (191) expounds Janet's views in the light of twenty-six personally recorded cases. Williams (175, 176, 179, 180, 183, 184, 187, 189) is an ardent supporter of Babinski's views, and has expounded them in a number of short articles. Mills (108) supports many of Babinski's views, which he considers to be very fruitful, but does not think that they contradict Janet's dissociation theory. He holds that physical trauma and emotion are operative as well as suggestion, and believes that vaso-motor symptoms may result from hysteria, as does Edgeworth (51). Dercum (37) throughout opposes Babinski's views, and explains hysteria as a retraction of neuron processes. Dana (34) regards hysteric symptoms as indicating a "wearing out of the psychic machinery, due to some metabolic cell degeneration produced by a teratological defect." Savill (147), who is the leading authority in London on the psycho-neuroses, holds that hysteria is a disease of the sympathetic nervous system.

Several attempts have been made at a *re-classification of the psycho-neuroses*. Dana (33) restricts the term hysteria to the severe cases with pronounced bodily symptoms, and divides the psycho-neuroses into—1, Neurasthenia; 2, Abortive types of the major psychoses (*e.g.*, manic-depressive insanity); 3, Phrenasthenia, including (*a*) Hysteria major, (*b*) Hypochondriacal Psychasthenia (usually diagnosed as hysteria), (*c*) Obsessive Psychasthenia. Dercum (37) divides them into—1, Neurasthenia; 2, Neurasthenoid conditions; 3, Symptomatic neurasthenia; 4, Hysteria; 5, Hypochondria. Walton (171) groups all cases of tic, hypochondria, neurasthenia, hysteria minor, *folie de doute*, and mild manic-depressive tendencies under the term "obsessive psychosis," considering the obsessive feature to be the fundamental one.

Stress is laid on the mental side of *neurasthenia* by Donley (44), Drummond (49), Lane (91), J. K. Mitchell (110) and others. Lane considers that some depressing emotion, and not overwork, is the cause of neurasthenia. Savill (145) attributes neurasthenia to toxins absorbed from the teeth and intestines. Courtney (31) regards psychasthenia as a *forme fruste* of *petit mal*, and closely allied to epilepsy. It need hardly be said that the sexual genesis is not referred to by any writer. Booth (8) contends that coitus interruptus is an important cause of psycho-neurosis, but draws no clear picture of the symptoms that result.

The first of Adolf Meyer's papers referred to (99) is a long and sympathetic review of Bleuler's *Affectivität, Suggestibilität und Paranoia*; he opposes any over-dogmatic separation of the emotional and intellectual

functions. In this, as in his other papers, Meyer uses his influence powerfully and consistently in support of the importance of the *psychogenetic point of view*. Two matters, however, make it difficult to review his work or to convey a just appreciation of its significance, first, in that his influence has been mainly exerted in personal teaching or in society discussions, and, secondly, in that his publications on the subject include no independent papers, but are comprised either of comments on various German writings, in the form of a review, or of abbreviated accounts of papers read before societies. His writings are very general in character and do not deal technically with the actual mechanisms of psychogenesis. Anyone, therefore, who knew only of his writings would be liable to under-estimate the value of his influence. The main theses he develops are: the great importance of adopting a general biological point of view, especially in contrast with the histological one, and of testing abnormal manifestations as different forms of reaction to the environment. Speaking of *dementia præcox* he says (101): "The symptoms appear as perfectly natural results, not of abstract and so far undemonstrated auto-intoxications, or supported merely by fragments of histological knowledge, but of habits of function and mental activity which may in part open a chance for correction. . . . The general principle is that many individuals cannot afford to count on unlimited elasticity in the habitual use of certain habits of adjustment; that instincts will be undermined by persistent misapplication, and the delicate balance of mental adjustment and of its material substratum must largely depend on a maintenance of sound instinct and reaction-type. . . . At first, perhaps, there is merely an excess of substitutive reactions, such as occur also in the normal, a shirking and scattered and distracted slurring over of the difficulties, secretiveness, instead of a frank ventilation and correction by joining the activities of the normal, a habit of excusing carelessness and lack of determination by hypochondriacal complaints or fault-finding with others, or the habit of passing over difficulties by imaginative thoughts, or mere praying, or pondering, or other expedients which as a rule help successively over an individual disappointment, etc." He joins issue with Bleuler (105), who, he says, agrees with Kraepelin in regarding general paralysis as the obligatory paradigm of the psychoses; the ætiology of *dementia præcox* he sums up as a conflict of instincts and habits. In psycho-pathology he lays especial stress on "abnormal ways of dealing with the situations of life, and on the tendency towards false adjustments," and (105) describes six reaction-types of disorder: (1) The reactions of organic disorders; (2) Delirious states with

dream-like imaginative experiences, hallucinations, especially of sight, with deficient orientation; (3) The essentially affective reactions; (4) Paranoic developments, of six grades; (5) Substitutive disorders of the type of hysteria and psychasthenia; (6) Types of defect and deterioration.

Macfie Campbell, an assistant of Meyer's, has in a very clear article (15) expounded Meyer's views of dementia præcox, and gives an account of five cases. The psychosis is "the culmination of a long-continued period of unhealthy biological adjustments in individuals who constitutionally are apt to meet their difficulties in an inadequate manner." August Hoch (67, 68) also lays great stress on psychogenesis in the psychoses. In dementia præcox (69) he states that in 50 per cent. of the cases he has discovered evidence of a peculiar "shutness" in the personal reactions before the outbreak of the malady. Ricksher (141) has applied Stern's *Aussage* methods in dementia præcox, and finds that the ability to reproduce the stimuli depends directly on the ability to concentrate the attention.

Campbell (15), Donley (46), Hart (62), Meyer (99, 103, 104, 105), and Putnam (136) deal with the relation of *philosophic conceptions* to psychiatry. Meyer (104) defines mind as "a sufficiently organized living being in action." Hart's paper is especially lucid and penetrating. He develops the point of view represented by Ostwald, Mach, and particularly by Karl Pearson, and distinguishes clearly between the empiric conceptions of scientific idealism and the absolutist view of various schools of metaphysics. His remarks on the practical application of these principles to the problems of research in psychiatry, and his criticism of the materialistic views current in psychiatric circles, especially deserve to be read. Peterson (121) argues that the corpus striatum is the seat of consciousness.

Finally, an essay of Chamberlain's (18) should be mentioned, in which is contained an interesting collection of the beliefs and superstitions about night in folk-psychology.

IV.—PSYCHO-ANALYSIS.

In the English literature I have been able to find only one reference to Freud's work, and none to Jung's. In America, on the other hand, a considerable number of articles on the subject have appeared. Psycho-analysis is discussed in most articles on psychotherapy, though in two recent extensive reviews of the subject, by Mills (106) and Münsterberg (112), it

is not mentioned. The writings may be divided into three groups according as they support Freud's views, adopt an attitude of suspended judgment or of indifference, or oppose it.

To the first of these groups* belong those of A. A. Brill and the present writer. Four papers have been published, one by Brill (12), and three by the present writer (84, 88, 90), expounding Freud's views. They contain nothing that is not familiar to readers of the *Jahrbuch*. In a paper on the psycho-pathology of everyday life (11) Brill records an interesting collection of some twenty instances illustrating Freudian principles. One of them may be quoted. On thinking of a certain patient in whom he had been very interested, and with whose case he had spent a great deal of time, Brill found himself unable to recall the patient's name, and decided to make a self-analysis to test the method. The case had been an unusual one, and after taking great pains he had written an account of it for publication. Just when this was ready, his chief informed him that he wished to publish the case himself at a society meeting, which he did, to Brill's considerable disappointment. The chief was, however, at the last moment prevented from personally reading the paper. In five hours' analysis Brill filled over two dozen sheets with a record of the free associations that occurred to him, but at first in vain. He then observed that two thoughts, apparently unconnected with the subject, kept on recurring to him. The first one, which came back to him twenty-eight times more often than any other, was a vivid memory of an actual scene in which his chief had shot at a rabbit but missed it. While he was ruminating on this memory the patient's name that was being sought suddenly flashed up. It was *Lapin* (rabbit). The scene had symbolically expressed his chief's failure to "bag the rabbit." The other thought that kept recurring was the name of another patient, Appenzeller, who was suffering from the same malady as the first one, and the first part of whose name phonetically closely resembles the French word *Lapin*. In a short paper (82), which was read at the Salzburg Congress, the present writer gives an account of the mechanisms of rationalisation and evasion, by which a subject invents a plausible explanation for a given belief or action that has really been determined by some unconscious process.

* Since this date a considerable number of favourable articles have appeared. See 'Journ. of Abnormal Psychology,' vol. iv, Nos. 5, 6, vol. v, Nos. 2, 3, 4; 'Amer. Journ. of Psychology,' January and April, 1910; 'Psychol. Bulletin,' April, 1910; 'Amer. Journ. of Insanity,' July, 1910; 'Journ. of Nerv. and Ment. Dis.,' May, 1910; 'New York Med. Journ.,' April, 1910; 'Interstate Med. Journ.,' July, 1910; 'Maryland Med. Journ.,' June, 1910; etc., etc.

Psycho-analytic accounts of four cases have been published, two by Brill and two by the present writer. The former two were cases of dementia præcox, which had been investigated at Burghölzli. The first of these (9) occurred in a bank clerk of thirty-nine, in whom the first outbreak of insanity had taken place some nine months previously. He had had two acute crises, lasting three days and a week respectively, of the delirious confusional, dreamlike type. The intervening and succeeding periods were marked by great restlessness, delusions and hallucinations. Brill relates the reactions to fifty-six association test-words, and gives a short analysis of each of these; of the responses twenty-two concerned erotic complexes and seven religious ones. The patient's father was very religious, the patient was an atheist. The religious influences of childhood expressed themselves in the crises by the patient feeling himself forced by a magnetic power to kneel and repeat "Our Father" hundreds of times, identifying himself with Christ and his father with God. He also felt himself under the power of Isis and Osiris, Osiris being the name of a wealthy banker who had recently died and from whom he expected money. The general psychogenesis of other manifestations is also described. The second case (10) was that of a law student and promising journalist, aged 20 years, who had, after a short period of depression arising from disappointment in a love affair, attempted to commit suicide. He fired five shots at himself, but hit only a picture of Ibsen and a candle. He then passed into a delirious condition and repeatedly murmured to himself, "Where are the white horses?" After a period of dulness, apathy and somnolence, he recovered. Brill gives the analyses of a number of association reactions, which indicated that the love affair had not played the significant rôle in the outbreak of the psychosis that it had seemed to; for years before he had suffered from hypochondriacal ideas and self-accusation. The analysis of the attempt at suicide is especially interesting. The shots were symbolic actions, and were intended to kill the part of himself that he loathed. The candle was associated with a masturbation complex, and Ibsen, with whom he had unconsciously identified himself, with an egocentric complex. The cry, "Where are the white horses?" was of course taken from Rosmersholm, where they presage the hero's death. Brill adds a number of apposite remarks concerning the *apparent* senselessness of the manifestations of dementia præcox.

The first of the present writer's cases referred to (85) was one of hysteria that occurred in a man, aged thirty, who on his arrival in a Toronto hospital could give no account of himself, or tell us his name, his

country, or anything of his past life. The only name he could give was Bert Wilson, though he did not think this was his own. When his memory was brought back it was learnt that he had been a sea-cook for many years, but had recently settled down in New York State, where he now had a wife and child. Two months before he had lost his work and had left home to find another situation, leaving his wife with only a little money. He did not succeed, had to tramp long distances and do without food, and on reaching Buffalo he saw a navigation advertisement and took a boat crossing the lake to Toronto. In his despair he unconsciously identified himself with Bert Wilson, who was his senior (a sea-cook) on his first voyage, whom he had formerly envied, who had run away to sea as the patient did when a boy, whose wife maintained herself by keeping a lodging-house, so that he had no anxiety about her when away, who had once deserted and changed his name to escape detection, and finally, whose name nearly resembled the patient's own (Bert Williams). The symptoms illustrated a great number of the unconscious mechanisms in hysteria which are described. An instance of *Verwendung desselben Materials* and *Umkehrung* may be quoted. When asked the street in which the New York Station is situate (42nd Street), the patient answered first 24, then 28 ($24 + 4$), then 32 ($24 + 4 + 4$), and finally 26 ($24 + 2$); his street number in New York was 4. A short discussion of the nature of amnesias is added. The second case (87) was one of manic-depressive insanity in a woman aged 39 years. Erotic and religious complexes revealed themselves in various delusions, symbolic actions and flights of ideas. For her childlessness she blamed her husband, partly on account of his relative impotence, partly on account of a gonorrhœal salpingitis from which she had long suffered. She had had illicit relations with other men that had caused her much remorse. Religious appeals to forsake her evil ways and lead a new life she interpreted as a revelation indicating the error of her past sexual life and advocating a new form; this new way, for various reasons, she imagined to be the fellatorism perversion. She then identified the Holy Communion with fellatorism, and obtained sexual gratification from going through imaginary performances of this ceremony. The other symptoms, such as delusions of being poisoned, refusal to take food, intense excitement, etc., are analysed and traced to the same group of complexes. In one delusion, concerning a watch, she identified this with the uterus because "it has works inside that keep regular time (s) and it needs a key to wind it up."

In the second group may be counted five articles. These include a

short account by Collins (21) of psycho-analytic treatment, in which no opinion is expressed as to its merits, a general account of complexes by White (173), an article by Peterson (122) in which a page is given to a description of Freud's views on psycho-analysis, dreams, insanity and everyday life, and two articles by Putman* (135) and Linenthal and Taylor (94) respectively, in which is given an account of attempts to apply psycho-analysis. The latter two papers are on the whole sympathetic, and several cases are recorded, in which, however, the psycho-analysis is of a very elementary kind.

The third group is the largest.† The accounts given of psycho-analysis are very brief, usually taking up less than a page, and are often distorted, as for instance in Collins' article (21) where it is said that Freud (there throughout called Freund) relies on hypnotism, or in Scott's (150) where it is said that "the normal reaction of an emotion is converted into voluntary movements of defence, which may then survive as habit spasms." The adverse criticisms are rarely written in a personal tone, and are evidently based on ignorance of the subject. Prince's criticism of Freud's views of the *Unbewusste* have been mentioned above: he denies (131) that the therapeutic successes of psycho-analysis are due to the making conscious of repressed mental processes, for "if nothing more were done the patient would still not tolerate them and would push them out again." The results are due to the general re-education, to the introducing of new ideas and feelings into the complexes. Pierce Clark (19) says "Freud's method is of great benefit in hysterics, but it is not widely applicable in general disorders of the minor neuroses until the sexual idea is eliminated." Allen (I) sums up in exactly the same words, evidently copied from Clark; in describing the method he explains that "the physician should be a man of morality, yet (*sic*) a man of the world." Courtney (32) says that Freud has an *idée fixe* on the subject of sex; he adds: "the theory applies only to a certain unwholesome type in whom any unusual accident in the sexual sphere may lead to hysteria. There are extremely few cases in which education and environment, coupled with the individual's own power of inhibition, do not shield him from the dangers which may accompany the externalization of the instinct in any of its forms." Edes (50) says that "Freud's method invites an attitude of confidential trust evoked by long-

* In later papers Putnam has expressed his cordial agreement with Freud's views, as have Adolf Meyer, August Hoch, Macfie Campbell, and others.

† As this review was written for the *Jahrbuch*, whose readers are familiar with psycho-analysis, the adverse criticisms are here quoted in their naked absurdity, without any comment; they are throughout based on an entire ignorance of the subject.

continued and careful questioning. This tedious questioning is almost certain to implant and vivify ideas of the very kind which it is desirable to get rid of." Schwab (149) says that Freud's treatment is useless, because it is doubtful if there is such a thing as subconscious activity. Ring (142) writes of psycho-analysis as the method of Janet and Freud, and objects to Freud's theories that they do not take account of the emotions of fear and anger, fear being the most important ætiological factor in the psycho-neuroses. The most inept criticisms, however, are those by Dercum (38), Savill (147) and Scott (150). Dercum, referring to Freud's theory of obsessions, writes: "Others than myself have dwelt upon the glaring inconsistency of the sexual immaturity of children and the intrinsic biological improbability of this theory. Perhaps Freud has himself been impressed by this fact, for of late years it would appear that he has retreated to the age of puberty, attempting to save the situation, however, by saying that the memory of these sexual events is projected from puberty into the period of childhood Next is the all-important factor that Freud's explanation leaves out of consideration all the obsessions which obviously and clearly have a non-sexual origin. What shall we say, for instance, of the obsessions present in the cases of the traumatic neuroses, which in this country may be fairly said to greatly outnumber all others? What shall we say as to cases of the special fears the origin of which can be clearly traced to occurrences non-sexual in character? What shall we say of the obsessional states which make their appearance in middle life or toward old age? By what possibility can these be ascribed to infantile sexual aggressions? Like Edes, Ring, and many others, Dercum imagines that Freud's method consists in the questioning of patients about their sexual lives. "Such questioning must be persistent and insistent, and, aside from the doubtful value of the results obtained, must be painful and offensive alike both to the physician and patient. Certainly, in persons of high social and moral make up, such a *séance*, if at all possible, must be intensely disagreeable, and if the truth be known the rehearsal of sexual details, repulsive and revolting probably does harm and not good." Savill (147) makes on the same page these two sets of statements, which may profitably be compared with each other. "Freud's investigations have a tendency towards the revival of long-forgotten sexual incidents. It appears to me that there is a good deal of danger both to the patient and to the physician in undertaking such investigations I cannot but regard it as a most undesirable thing for any medical person, and particularly for one of the opposite sex,

to make investigations into the dead memories of a sexual past. 'To my mind such a procedure would be hazardous, harmful, and wholly unjustifiable.' "Freud states that with a normal *vita sexualis* a neurosis is impossible. This does not accord with my experience, now somewhat considerable, of these neuroses. I have seen scores of neurasthenics and hysterics whose sexual life-history and constitution were absolutely normal." Scott (150), Professor of Psychology in the North-Western University, considers that the success of psycho-analysis is obtained by suggestion, and that those who use this method have by their ignorance of this fact been "hampered in their treatment, and have taken longer time for their cures than otherwise would have been necessary." On one occasion he demonstrated himself the truth of this opinion by applying "psycho-analysis" to a case. This is his account of it. "The patient was told (sic) that she had been guilty of sexual irregularities, that she had had sexual experiences which had undermined her health, and that her perfect cure was delayed by the fact that they had never been confessed. She seemed to believe this implicitly, her confession disclosed all the factors which even Freud would expect to find in a case of extreme phobia (distressing sexual experiences of youth, sexual perversion, sexual excess, as well as periods of sexual anæsthesia). At the conclusion of the confession she fell back into a condition of relief, which was the condition needed for the most perfect possible working of suggestion. . . . As an antidote to the rehashing of all this sexual filth the patient was hypnotized and total amnesia was suggested for all the ideas which had had a casual part in the history of the disease."

Jung's work is more widely known in America than Freud's and is more generally accepted there; in fact, it has met with practically no adverse criticism. Among the favourable reviews of it may be mentioned those by Meyer ('*Psycho. Bull.*,' 1905, p. 241; 1906, p. 275; 1907, p. 196; 1908, p. 273); Kirby (*ibid.*, 1907, p. 197; 1908, p. 270); Hoch ('*J. Ab. P.*,' June, 1906, p. 95); Coriat (*ibid.*, June, 1908, p. 137); Karpas (*ibid.*, December, 1908, p. 366), and Hart ('*Journ. of Ment. Sci.*,' 1908). The works of Bleuler, Riklin, Wehrli, and Binswanger are also included here. Demonstrations and expositions of his association methods have been published by Bailey (4), Henke and Eddy (65), Scripture (151), Town (168), and Yerkes and Berry (191), all of whom confirm his findings and conclusions. Peterson, both independently (119, 120), and in conjunction with Scripture (123), has given demonstrations of the psychogalvanic method. Prince and Peterson (129, 133) have used this method

to prove the existence of co-conscious ideas in a case of multiple personality. Sidis and Kalmus (160), in two articles that are not primarily concerned with psychological problems, have given an account of experiments which they maintain show that the psycho-galvanic reflex is the result, not of any change in the bodily resistance, but of independent currents set up by the emotional disturbance. Prince (130) accepts their results. Coriat (29) finds that the emotional disturbances are more readily detected in association work by an increase of frequency in the pulse-rate, best observed while the patient is in the hypnoidal state.

Two events of the past six months should also be mentioned in the present connection, namely, the lectures* delivered by Freud and Jung last autumn at Clark University, Worcester, Mass., and the publication of some of Freud's papers, and of Jung's 'Psychology of Dementia Præcox,' in translations made by Brill ('Journ. of Nerv. and Ment. Dis.'; Monograph Series).

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Dementia Præcox.*

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INTRODUCTION.

Dementia præcox is a term which has been applied by Professor Kraepelin, of Munich, to a definite group of mental disorders commencing usually at or about the period of adolescence and terminating, in the majority of cases, in dementia.

This observer admits that the variety of clinical forms included under this definition is very great, and that the connection between them may not be readily perceptible, but asserts that there are certain fundamental symptoms which can be recognised in all cases which justify the state-

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ments he has made. Many authorities, however, object to the use of the term on the ground that sufficient evidence has not been produced to warrant the recognition of dementia præcox as a definite clinical entity, and this they state can only add to the confusion which already exists in the nomenclature of disorders of the insane.

I have had the opportunity of studying in the London County Asylum at Claybury a large number of cases similar to those described by Professor Kraepelin. I am convinced of the correctness of Professor Kraepelin's observations, and I believe that it is possible to recognise under this heading certain obscure cases which hitherto have defied a suitable classification.

I propose in this thesis to record the main features of interest connected with this form of insanity, and to add a description of some of the more important cases which have come under my observation.

DEFINITION AND HISTORICAL SURVEY.

Definition.—Dementia præcox is a psychosis essentially characterised by a special and progressive psychic enfeeblement commencing usually during adolescence, and culminating, as a rule, in the disappearance of all manifestations of mental activity, without ever compromising the life of the patient.

The onset of the affection is usually signalised by the manifestation of diverse neuropathic disorders, these being in turn followed by the appearance of psychic derangements of various types, such as excitement, depression, states of confusion and hallucinations.

The commencement at or about the period of adolescence, and a termination in a more or less complete dementia, are the most characteristic features of the malady.

Historical survey.—The earliest reference to a mental state resembling dementia præcox is in a small volume entitled "*Lehrbuch der Störungen des Seelenlebens*," written by Professor Heinroth, of Leipzig, and published in 1818. It is as follows:—"The whole appearance, the posture, the attitudes of the patient bear the stamp of this condition. His glance is lifeless, the face expressionless—except for a dulness which is the result of inactivity. His posture is one of languor, and his movements are slow and dilatory. . . ." This is his description of one of the various forms of dementia, and he here anticipates the later conception of dementia præcox.

In 1863 Professor Kahlbaum described a form of mental disease occurring at puberty and rapidly terminating in dementia. This he called "Hebephrenia." In 1874 the same author described the condition known as "Katatonia," or the insanity of rigidity.

In 1871 Hecker contributed his work on "Hebephrenia," the chief features of which he describes as follows:—"Onset in close succession to puberty; the appearance alternately of melancholia, maniacal and confused states, a speedy psychic decline, with its finality in terminal dementia, which may be anticipated from the first."

In 1891 Pick, under the heading of dementia præcox, described cases, including hebephrenia, characterised by maniacal symptoms followed by melancholia and rapid deterioration.

The latest and most original work has been furnished by Professor Kraepelin, who has connected certain maniacal and depressed states with stupor and catalepsy, bizarre attitudes with delusions and hallucinations, in order to form one comprehensive group—dementia præcox—whose termination is a special form of mental reduction, and has extended the term dementia præcox to include the Hebephrenia and Katatonia of Kahlbaum, together with certain forms of paranoia which undergo early deterioration.

SYMPTOMATOLOGY.

The varied character of the symptoms which are met with in this affection renders their description a matter of considerable difficulty. It may here be stated that their very complexity has been the subject of the keenest criticism at the hands of those who are opposed to Kraepelin's teaching.

The following varieties of dementia præcox have been described:—

1. The simple dementia, or heboid phrenia of Kahlbaum.
2. Hebephrenia.
3. Katatonia.
4. Paranoid forms.

To this list may be added a *simple form* described by other writers.

It must be admitted that these divisions are largely artificial. Professor Kraepelin himself says: "No rigid line can be drawn between the divisions, because the cases run into each other and overlap continually. There are whole series of recurring forms, but between them lie such a variety of cases, that, in spite of all effort, it is impossible to classify each case without exception, into a given category." From a perusal of his

lectures, it is quite clear that he regards these divisions not as separate entities, but as varieties of the same condition; and he has further emphasised the necessity of classifying the psychoses upon their course, and termination, and not purely on their symptomatology. He has tersely described the diagnostic point or symptom of this disease to be "a peculiar and fundamental want of any strong feeling of the impression of life with unimpaired ability to understand and to remember." In addition to these types or sub-divisions there are certain symptoms which are common to all cases. The first change which is usually noticed is a desire for solitude and loneliness, with some uncertainty and irritability of temper. There is a lack of interest in work and pleasure; and an emotional deterioration shown by bluntness of feeling towards incidents which formerly would have caused excitement, joy or grief. There may be a marked decrease in affection, and a loss of the sense of decency. This lack of interest and loss of emotion gradually becomes more marked, and in from two to three weeks or months there is an apparent complete indifference to all that is taking place. But cases in which the mental condition has improved under treatment have told me nearly all that had happened while they were in this state, and have explained their indifference by stating that they lacked all power of initiating movements, and thus were incapable of showing that they appreciated what was taking place. One patient (W. D.) was admitted in a state of *flexibilitas cerea*. He never spoke, never initiated a movement, and remained in any position in which he was placed. At the end of three months he suddenly spoke. He remembered nearly everything that had happened and gave a good account of all that had taken place since his admission. He knew the names of doctors, attendants and patients, and told me the nicknames of certain patients and appreciated the humour of these nicknames. His explanation was that he was unable to initiate any movement although he desired to do so.

Another patient (H. M.) was very similar. Neither of these patients had any feeling of hunger during this state. The latter patient had certain stereotyped movements. He said afterwards that he had no desire to do these but was quite unable to control his actions. Neither of these two cases recovered.

Other patients, after the onset, develop impulsiveness, hallucinations or delusions, and other symptoms which will be mentioned under their appropriate headings.

The patients are well oriented in all respects and show no evidence of

clouding of consciousness. If closely watched, they may be seen to observe keenly all that is going on without giving any sign at all that they do so. One (Mr. C.) who had stereotyped movements, mutism and negativism, was persuaded after some difficulty to write answers which showed that there was no dulness of consciousness.

The memory is but little disturbed. The will power is lost and judgment is, without exception, affected. Although the patients can remember what they hear and what takes place, their train of thought suffers, and under strange circumstances they are helpless. There is a lack of all power of initiation. Patients may develop sudden impulses or stereotyped movements, but these are quite subconscious, even when the impulse is to self-destruction. The impulse to this is perfectly aimless. The normal mental state is never regained.

I. *The simple form.*—Patients suffering from this form are seldom seen in asylums. The condition usually commences about the age of 16–18 years, in a subject who previous to the onset of symptoms was considered a bright and intelligent child. The onset of this variety is insidious, and it may be quite impossible to fix its date, because initial symptoms are not appreciated at their true value. A lack of interest in surroundings and a desire for seclusion may be the first change noticed. There is a failing ability to assimilate new facts, a retarded mental intellect slowly progressing to dementia without the development of impulses, hallucinations, or delusions. The patients become semi-automatic, and are frequently conscious of their state. They may suffer from headache and insomnia, and may be the victims of vague fears and hypochondriasis.

II. *Hebephrenia.*—This form of dementia præcox is usually of more abrupt onset than the last, although the prodromal period may extend over several months, during which time the patient suffers from insomnia, headache, anorexia, and perhaps loss of flesh. The symptoms of the onset of the attack are generally confusion and depression.

These patients are liable to develop states of excitement or depression accompanied by systematised delusions, hallucinations and impulses, mystic ideas and eroticism. Kraepelin and Trommer have drawn special attention to the incoherence in speech and writing which is of special importance in the diagnosis. This is characterised by the persistence of ability for correct grammatical construction, the richness of unusual and new words, and the lack of meaning in both written and spoken language. This disordered language corresponds to the change in their manners and behaviour. The aspect of these patients, their attitudes, gestures, methods of eating and

drinking, and walking, are bizarre and artificial. Hallucinations and delusions may be combined with dulling of the emotions, childish idleness and senseless laughter, and usually mental enfeeblement is established within two years. Profound deterioration occurs in about 75 per cent. of the cases, and only 8 per cent. can be considered to improve.

III. *The katatonic form.*—This variety, like the other forms of dementia præcox, is usually sub-acute or chronic in its onset, and may be preceded by similar prodromal symptoms. Occasionally the onset may be sudden, the exciting cause being some severe emotional shock or fright. In these cases the patient may enter at once into a profoundly stuporous condition. Following the more or less vague symptoms of the prodromal period the typical symptoms of the disease develop, viz. katatonic stupor and katatonic excitement. Katatonic stupor is characterised by negativism and automatic obedience or suggestibility. Negativism is characterised by a resistance to all external intervention, any effort to place the patient's limbs in a particular position is strongly resented, and results in a condition of muscular tension. If one is successful in placing the limbs in the desired position they are immediately returned to their former state. Resistance may be carried to such an extent that the patients may refuse to eat, to dress, or to sit down. There may be voluntary retention of urine and faeces, and an insensibility to all external influence. No attention is paid to questions. The patient may remain absolutely mute, while sensory stimuli of considerable strength may be applied without eliciting any response. This condition of negativism to all outward influence is a marked symptom. It is often accompanied by the performance of certain movements illustrative of muscular tension, such as grimacing and frowning. A peculiar feature, known by the Germans as "*Snautzkrampf*," consists in a stereotyped movement of puckering up the lips and then protruding them rapidly, which movements may be repeated for hours. Quite the reverse of this picture is that of automatic obedience or suggestibility, which is characterised by the adoption of katatonic attitudes, in which the patients persist in maintaining the most extraordinary positions into which they may be placed (*flexibilitas cerea*).

Automatic suggestibility is further shown in some cases by a mechanical obedience on the part of the patients to do as they are told. Echolalia and echopraxia belong likewise to this group of symptoms.

In katatonic stupor there is lack of co-ordination in all movements, and muscular reaction is retarded. For example, when asked to shake hands the patients will usually very slowly put out the hand, and when it is

taken they never grip the proffered hand, and never shake it, and do not withdraw their own; at other times they take no notice. Dr. Stoddart regards as distinctive the ape-like character of the hands, and a peculiar handshake, the patient holding out the hand stiffly and straight, and frequently rudely withdrawing it at once. The method of writing is also peculiar. There is much delay in commencing, and patients have to be asked to write several times. They hold the pencil in whatever position it is put in the hand, making no effort to get it into the writing position; the paper has to be placed underneath the pencil. If paper and pencil are placed on the table in front of them, they make no effort to write. They write very slowly, with much hesitation, and with apparently great effort in forming each letter, and in completing, connecting and touching up what has been written. Repetition of letters, words and sentences is commonly present. Muscular fatigue soon becomes apparent. If the katatonia is profound, they cannot be induced to write. If it is less profound, they can be made to write with great effort; but they are very slow, and repetition is very marked. In cases with slight katatonic symptoms the first few answers are written fairly well; but the writing soon becomes slower, and they commence to repeat words and letters, and have to be stimulated frequently.

These attacks of katatonic stupor may alternate with phases of katatonic excitement. Here the condition of passiveness and stupor is replaced by increased psychomotor activity, and is characterised by the performance of purposeless actions, stereotyped movements and verbigeration. Most interesting is the continued repetition of the same movements; for example, patients will persist in walking round in a circle, or will clap their hands together for an indefinite period, or dance, gesticulate, and make grimaces. As an interesting example of this purposeless repetition of certain movements, I can recall to mind the case of a young male suffering from katatonic excitement, who was in the habit of seeking the corner of the room and there would proceed to beat the side of his head with his hand for hours together, varying this performance by spitting into his coat sleeve at intervals. The constant repetition of this action had completely worn away the hair from one side of his head.

The temperature of these cases during the acute stage may be raised to 100°-102° F.

IV. *The paranoidal form.*—This form is characterised by the rapid development of mental deterioration, with complete retention of consciousness for a considerable time. This is accompanied by delusions and

hallucinations and sensory phenomena which are the predominant symptoms for several years. The hallucinations of sight and hearing and the fantastic delusions of persecution and of grandeur may equal, even if they do not surpass, in their extravagance those of general paralysis of the insane. These are the features which characterise this form of dementia præcox. This condition differs from true paranoia in that it develops rapidly, that the fantastic delusions are not based on fact, and that prominent hallucinations are present. Paranoia, on the contrary, develops slowly, hallucinations are few, and the delusions are based on some actual fact which is misconstrued.

Recoveries in this group do not take place.

PHYSICAL SIGNS.

Most patients suffering from dementia præcox become emaciated with the onset of the disease. It is of interest that Pighini, conducting metabolic experiments on these cases, found that in the acute phase of the disease the results indicated an excessive metabolism and a destruction of the sulphurized and phosphorized proteids of the organism; in the more chronic phase, however, he found that this excessive metabolism abated. Later, under treatment they may regain and even exceed their normal weight, but they are liable to considerable fluctuations in this respect during the progress of the disease. Cardiac arrhythmia and bradycardia may be present; the pulse is usually small and feeble, the skin dry, the extremities cyanosed and cold. Constipation is always present and troublesome. The urine is scanty, of high specific gravity, and often contains excess of urates and phosphates. The knee-jerks are usually increased, and the tendon reflexes may be exaggerated. The cutaneous reflexes are abolished or feeble in 50 per cent. of the cases, and are always greatly diminished in the katatonic group. The pupils in most cases are widely dilated. They are equal and react to light and accommodation. In a few cases I have noted slight inequality or irregularity of the pupils.

A fine general tremor is present in several cases. Serieux has noted cases with exophthalmos and enlargement of the thyroid gland, but I have seen no cases with these symptoms. Before and during the onset there is a history of insomnia in all cases, and anæmia is very common.

In females menstruation is often irregular, and in some cases there is amenorrhœa.

In the katatonic cases there is dribbling of saliva from the mouth, but probably no increase of salivation, as all the secretions are retarded.

FREQUENCY.

Professor Kraepelin's observations lead him to believe that 14 to 16 per cent. of the total admissions to asylums are cases of dementia præcox, and those of Dr. Paul Serieux at the Maison de Santé de Ville Evrard are very similar. In this country the percentage is not so high, and this may be accounted for by the fact that the disease is not generally recognised by many English alienists. Further statistics must therefore be awaited before any correct indication of the frequency of dementia præcox can be obtained. My own belief, however, is that the figures given above underrate the frequency of the disease. This is borne out by a recent publication of Dr. Ryssia Wolfsohn, who in an examination of 2215 insane patients has discovered no less than 647 cases of dementia præcox, an average of 30 per cent. (23 per cent. males; 39 per cent. females).

AGE AT ONSET.

The average age of onset is between twenty and thirty years of age. I have seen only a few cases commencing outside these limits. Of 296 cases observed by Professor Kraepelin, 60 per cent. began before the age of twenty-five. The age of onset further appears to vary with the type of malady. For example, 72 per cent. of the hebephrenic forms, 68 per cent. of the katatonic, and 40 per cent. of the paranoidal forms, are stated to commence before the age of twenty-five.

Dr. Serieux, who has studied 50 cases which have come under his own observation, gives the age of onset as follows :

From 15 to 20 years	.	.	.	9 cases
„ 20 „ 25	„	.	.	14 „
„ 25 „ 30	„	.	.	12 „
„ 30 „ 35	„	.	.	7 „
„ 35 „ 40	„	.	.	8 „
				Total
				50

Dr. Bolton from a study of 100 cases states that the average age of onset varies from fifteen to thirty years in males, and from sixteen to thirty years in females.

SEX.

The disease appears to be equally common to both sexes.

COURSE AND TERMINATION.

Cases of dementia præcox never recover their normal mental state. Under favourable circumstances, certain patients may be brought back to a state approaching the normal, owing to their greater recuperative energy and reparative powers, but they differ entirely from cases of acute mania and melancholia in that they never regain their former state. A case of acute mania may recover and in no way differ from the condition which existed before the attack. This is not so with cases of dementia præcox. The acute stage of excitement with delusions and hallucinations or the state of katatonia, after a few months or even a year passes off and there remains a state of mental enfeeblement, which may be followed by another acute attack after a lapse of two or more years. This state of mental enfeeblement may be slight or more profound. Such patients may at first sight appear to be normal. They carry out simple tasks allotted to them, and are capable of giving a fair amount of attention to the ordinary routine of life, but a close examination shows a loss of judgment, a retardation of mental activity, a state of childishness, a marked diminution of affection, absence of desire and curiosity; and further a satisfaction with their condition. Others have an absolute lack of interest in everything. They have to be dressed and at times fed, and yet show that they know where they are, and that they understand and appreciate all that is taking place. Certain of these cases in which the dementia is less marked have been discharged to the care of friends, but they have not recovered.

Cases of dementia præcox, especially those which display the katatonic form, are especially liable to pulmonary and intestinal tuberculosis.

I have had the opportunity of examining the post-mortem records of sixteen consecutive cases which died at the London County Asylum, Claybury. The table on page 158 shows that in fourteen of these cases death was due to tuberculosis, and the average age at death was twenty-five years.

The cases which escape pulmonary tuberculosis live, under asylum treatment, fairly healthy lives, suffering at times from œdema and other signs of cardiac weakness from which they recover as a rule with rest and appropriate treatment. A large number of incurable cases whose physical condition is quite satisfactory, can usually be found in asylums. Figures have been given with regard to the prospect of mental recovery in the various forms of this disease. The hebephrenic is regarded as more

Initials.	Sex.	Age at Death.	Cause of Death.
G. S.	M	24	Tuberculosis. Both lungs extensively affected. Ulceration of small intestine. Liver, spleen and kidney affected.
C. H.	M	35	Tuberculosis. Both lungs, and large and small intestine extensively affected. Caries of sacrum — psoas abscess.
E. E. N.	M	35	Tuberculosis. Both lungs extensively affected.
H. F. R.	M	20	Tuberculosis. Both lungs, large and small intestine extensively affected. Liver and kidneys affected.
H. G. S.	M	23	Tuberculosis. Both lungs, intestines and peritoneum affected.
C. J. H.	M	23	Lobar pneumonia. <i>No tuberculosis.</i>
F. B.	M	27	Tuberculosis. Both lungs extensively affected.
C. C.	F	27	Cardiac failure. Bronchitis. <i>No tuberculosis.</i>
M. D.	F	28	Tuberculosis. Both lungs, intestines and peritoneum affected.
M. R.	F	17	Tuberculosis. Both lungs and intestines affected. Tubercular salpingitis.
F. L. M. O.	F	27	Tuberculosis. Both lungs, intestines and mesenteric glands affected.
M. A. H.	F	27	Tuberculosis. Both lungs and intestines affected.
J. B.	M	24	Tuberculosis. Both lungs—miliary.
A. R.	M	23	Tuberculosis. Both lungs—miliary.
C. W.	M	24	Tuberculosis. Miliary—both lungs—liver—spleen—kidney—bronchial glands.
F. W. S.	M	23	Tuberculosis. Both lungs extensively affected.

Total cases, 16. Average age at death, 25.

Tuberculosis caused 14 deaths, Lobar Pneumonia 1 death, Cardiac Failure 1 death. *87 per cent. died from Tuberculosis.*

serious than the katatonic. In the former variety 75 per cent. of the cases are stated to reach profound mental deterioration, and only 8 per cent. to recover. With regard to the katatonic state, 86 per cent. of the cases lapse into profound mental deterioration and only 13 per cent. recover, and even these show some peculiarity. No recoveries are stated to take place in the paranoidal group. Roughly 25 per cent. of all cases are said to show a greater or less degree of improvement, but I know of no symptoms from which we can conclude that this improvement is about to take place. My own opinion is that there is no real recovery from this affection. The apparent recoveries are probably due to remissions which sometimes occur and may lead to erroneous conclusions. I have myself seen cases which have been discharged as recovered, only to return in the space of a few months or years with a fresh attack, and to terminate in dementia.

TREATMENT.

The most suitable treatment is rest in bed, with isolation from home, friends and surroundings. To this end a trained nurse is essential. The

pulse and weakness of the heart sounds point to a condition of profound mental and physical exhaustion. Cleanliness and a simple nourishing diet, with open-air treatment where possible, are of the greatest service. After some months, when the bodily condition has improved, the patient may be allowed to get up and take gentle exercise in the fresh air. A warm bath should be given daily. I have tried electrical treatment in several cases but with no appreciable results. I know of no evidence that serum therapy or organo-therapy has had any beneficial effect.

Treatment for gastro-intestinal intoxication has met with no success, and the administration of thyroid and ovarian extract has produced no beneficial results.

PATHOLOGY.

Changes in the brain.—Sufficient cases have not been examined to allow of any definite conclusions being drawn regarding the pathological changes found in the brain. The macroscopical appearances are usually normal, Parchoppe alone stating that there is atrophy of the anterior two-thirds of the hemisphere and consequently a loss of weight of about 140 grm.

Dr. Mott has reported the microscopic changes in a case of dementia præcox in the 'Archives of Neurology,' vol. iii; he states that there appeared to be a deficiency of pyramidal cells in all regions. The Betz cells showed a marked deficiency of chromophilous substance, the nuclei being swollen, clear and pale, irregular in outline and often eccentric. Throughout the whole cortex and subjacent white matter there could be seen young actively dividing neuroglia cells, especially in the deeper layers. They were not found in the most superficial layers as in general paralysis and alcoholic dementia. He further states:—"Whether these changes in the large Betz cells can be associated with the katatonic condition, and whether this deficiency of stainable (nucleo-proteid) substance in the deeper layers can be in any way correlated with Dr. Koch's chemical observation, it is impossible to say."

Klippel and Thermitte have concluded from histological examination that there is no inflammatory reaction or any evidence of diapedesis in the coats of the vessels of the brain and spinal cord, the changes being entirely confined to the neurones of the association centres, and consisting of atrophy of the large pyramidal cells, with the exception of those in the motor-zone, and a granulo-pigmentary degeneration of the same cells, with a diffuse chromatolysis.

De Buck and Deroubaix from an examination of eight cases state that

the principal lesion consists of a pigmentary degeneration together with a gradual atrophy of the neurones, which results in a complete disappearance of the nervous elements. The layers of the cortex most affected are those of the large pyramidal and polymorphic cells, the vessels being only slightly affected. The authors suggest that these lesions are due to an autotoxic action on a predisposed soil, and from an anatomical point of view they conclude that dementia præcox resembles closely the exogenous toxic psychoses and especially that form which is produced by alcohol.

Nissl has found profound changes in the cells, which he has described under the name of *destruction du noyau*. A large number of cells, he states, appear to be destroyed, but there is no atrophy of the grey matter. The deep strata of cells (neurogliales), small and large, show signs of degeneration. The grey matter is, moreover, studded with large nuclei of neuroglia cells.

Gonzales has described the following changes in a case of dementia præcox:—Atrophy of the cells of the Rolandic areas, frontal lobes, pons, bulb and cord, with increase of neuroglia. There was a state of pigmentation observed in the cells of the motor areas and in the pons and medulla. In the Rolandic area the pigment was at times sufficient to occupy the entire cell body, though usually it only involved the periphery. He claims to be the first to describe this marked pigmentary cellular change in dementia præcox. The case was a married woman, aged 26 years. Regarding the other organs of the body Dide has also noted changes in the liver, and, according to him, dementia præcox is a subacute or chronic mental syndrome of toxic infectious origin. In the hebephrenic and katatonic varieties of dementia præcox, chronic enteritis is common. He states that the liver showed fatty degeneration in all cases. He considers that the decrease in urea observed in katatonia is due to hepatic insufficiency. He also states that tuberculosis is very common in hebephrenia and katatonia.

The chemical examination of the brain in dementia præcox.—The chemistry of dementia præcox has been studied by Koch and Mann, and their results tend to show that in this disease there is a disordered sulphur metabolism. A comparison of the chemical composition of normal brains at different ages has been made by these investigators, in which they indicate that as the adult age is reached, a highly complex (water insoluble) organic sulphur compound, *lipoid sulphur*, is formed at the expense of water soluble organic and inorganic sulphur compounds. Comparison with the normal shows that the brain in dementia præcox is lacking in

lipoid sulphur and the water soluble organic sulphur, while at the same time there is an increase in the amount of inorganic sulphur. The fact that Pighini has recently shown that there is an increased excretion of the water soluble organic sulphur in the urine in this disease, further points to the probability of a disordered sulphur metabolism, due to a general inherent bodily deficiency for oxidation processes.

Changes in the blood.—Pighini and Paoli have described special changes in the red blood corpuscles by the use of a special method of staining. Other changes described by them are:—

1. A hydræmic condition of the blood.
2. An occasional leucocytosis with increase in the polymorphonuclear leucocytes and of the blood platelets.

The authors state that the changes they have described do not indicate a degenerated condition of the cells but a physiological one, and they claim that their investigations support the theory of Kraepelin that dementia præcox is due to a disturbance of the organic metabolism.

Dide and Chénais have also investigated the blood in this disease. They say that it is difficult to deduce any definite conclusions, but one conclusion is sufficiently clear, that in twelve of their cases there was an increase of the eosinophiles. The authors state that in their cases the percentage of eosinophiles rose as high as 3 to 4 per cent., and this they regard as an eosinophilia. It need hardly be mentioned that their conclusions based upon this percentage of eosinophiles are quite incorrect and unjustifiable. Such a percentage of eosinophiles in the blood is quite normal, and there are few competent pathologists who would take any serious notice of the rise of eosinophiles in the blood until a percentage of 8 per cent. was reached.

Dr. Lewis Bruce refuses to accept dementia præcox as a definite entity and describes both hebephrenia and katatonia and dementia paranoia separately under the head of insanities of toxic origin. He describes katatonia as a distinct disease which passes through three stages, viz.: 1. The stage of onset. 2. The stage of stupor. 3. The stage of excitement. In typical cases he describes a distinct febrile attack which ushers in the stage of stupor. The leucocyte count shows a moderate persistent hyper-leucocytosis with increase in the polymorphonuclear leucocytes and large mononuclear cells. At the termination of the acute stage and just prior to the onset of stupor, he states that there is a sharp rise of leucocytes, the increase being chiefly in the polymorphonuclear leucocytes. A transient eosinophilia occurs in every case

according to this writer. I have carefully examined the blood in twenty cases of dementia præcox, but I was unable to confirm these observations. I made use of the Thoma-Zeiss hæmocyto-meter and of stained blood films. In no single instance did I find the number of leucocytes to exceed 8000 per cubic mm., nor did I find in the stained films any decided evidence of an excessive increase of the eosinophiles. A slight degree of anæmia was present in the majority of cases.

Examination of the cerebro-spinal fluid and blood.—In conjunction with Dr. Rae Gibson I have investigated the cerebro-spinal fluid withdrawn by lumbar puncture from cases of dementia præcox, paying special regard to the following points:—

1. The presence of micro-organisms.
2. The presence of protein, as evidenced by the Noguchi test.
3. The presence of cells in the deposit of the centrifuged cerebro-spinal fluid.

We have examined the cerebro-spinal fluid withdrawn by lumbar puncture during life from thirty cases of dementia præcox, and obtained a negative result in twenty-three cases after we had improved our technique. We are therefore forced to the conclusion that the reported discovery of any organism in the cerebro-spinal fluid in dementia præcox should be regarded with great caution, and in the light of the difficulties we have encountered, we would suggest that any such organism may be the result of external contamination.

The Noguchi test for proteins yielded a negative result in all fluids examined that were free from blood, and the examination for cells in the centrifuged deposit of the fluid was also negative.

Using the same technique we also examined the circulating blood for the presence of micro-organisms. About 5 c.c. of blood was removed from the patient; the greater part was placed in flasks containing 100 c.c. of sterile broth, and the remainder distributed among various media. In the twenty cases examined we were unable to detect the presence of any organisms.

Dr. Lewis Bruce has also made an extensive bacteriological examination of the blood in this disease, and he states that on one occasion he was able to isolate a streptococcus from the circulating blood; this organism was agglutinated by the blood-serum of fifteen out of twenty cases of that disease, *i.e.* in 75 per cent. He considers that the agglutinin frequently present in the blood of patients suffering from katatonia is a specific agglutinin. Serum treatment so far, he says, has produced no result. A

goat was immunised to the streptococcus and the serum of this animal injected. Beyond a fall of temperature in the acute cases, there was nothing worthy of note. Rabbits experimentally infected with the streptococcus intra-venously or by the alimentary tract developed malaise with irregular temperature, increased skin reflexes, and mental hebetude. The disease terminated naturally in about six weeks with the establishment of immunity to the organism.

The chemistry of the urine.—Pighini has obtained the following results from the examination of the urine of sixteen cases of dementia præcox. In all the cases the urea was considerably below normal. The density was notably increased in thirteen of the cases. The phosphates were normal, and in fourteen cases the chlorides were in excess. Albuminuria was only found in one case, and then was intermittent. Urobilin was present in one case. Indican and biliary pigments were absent. The later observation of this author on the increase of neutral sulphur in the urine has already been mentioned.

A consideration of the statements which have been put forward by the various authorities mentioned above will, I think, make it evident that the pathology of dementia præcox is at present very imperfectly understood. The histological appearances of the cerebral cortex are by no means distinctive when a comparison is made between them and those found in general paralysis of the insane, in which disease the histological appearances are very distinctive and diagnostic. Chemical analysis of the brain substance appears to yield more hopeful results, and I am of the opinion that in this direction there lies a great field for research, both in this disease and in all other forms of insanity, especially with the advance of our knowledge of the chemical constituents of the brain.

ETIOLOGY AND PATHOGENESIS.

The cause of this disease is as yet but little understood. Two main theories, however, must be mentioned: (1) That the disease is due to an inherited instability of the nervous elements; (2) that the disease is of toxic origin.

Prof. Kraepelin has found a neuro-psychopathic heredity in about 70 per cent. of the cases of dementia præcox, while Christian estimates that this can be obtained in 43 per cent. of the cases. I have found it present in every case where I have been able to obtain an extensive family history.

Dr. Ballet, of Paris, is of the opinion that constitutional predisposition is the most important factor in its production. In seventeen cases of this disease he was able to trace either a hereditary predisposition or some personal peculiarity in the patients themselves.

Dr. Ryssia Wolfsohn has made special inquiries into the hereditary transmission of this form of insanity. He selected 550 cases of dementia præcox upon which to study the influence of heredity. In 56 patients no heredity was found, but it was traced in 494 cases (235 males and 259 females), or in 91 per cent. of the male patients and 85 per cent. of the female patients. His deductions are as follows :

(1) A hereditary taint has been found in 90 per cent. of the cases (male and female) of dementia præcox.

(2) Of the four factors, insanity in the relatives is the most frequent, being about 64 per cent., after which come nervous diseases, then alcoholism, and lastly, eccentricity of conduct.

(3) In 34 per cent. of all the cases there was a combination of causes, especially insanity with alcoholism, and insanity with nervous diseases.

(4) When alcoholism, nervous diseases, and abnormal character appear as hereditary causes no especial direction of the form of dementia can be made out, while the transmission through insane relatives seems in some degree to incline to the katatonic and the paranoidal form of the dementia.

(5) No connection can be traced between the hereditary taint and the severity of the symptoms of dementia præcox.

The breaking down of the neurones is due to some cause which is best included under the term *stress*. This stress may be great or slight according to the inherent resistance of the brain cells, the more faulty the organism the less the stability and the less stress required to reach the breaking point. The advent of puberty in itself constitutes a stress, and there is superadded at this time the greater strain of education and the worries of obtaining a livelihood. Undoubtedly the period of adolescence is one of the most dangerous, when the emotions and physical powers are undergoing a new and wonderful development, as it is at this period that the least stable succumb. Other causes of over-exertion and of physical and moral exhaustion, such as menstrual disorders and the puerperium, have an unquestionable influence. Masturbation has been held to be an important factor in the production of the disease, but it is more probably a symptom than a cause. I have found a history of alcohol in one case only, and in no case has there been any history of acquired syphilis.

On the other hand, the exciting cause may be an auto-intoxication, possibly arising from some disturbance of the sexual glands, or from some functional insufficiency of the ductless glands, causing a bio-chemical change which has a toxic effect on the higher nervous mechanism. Professor Kraepelin has advanced the theory that the disease is due to an auto-intoxication acting upon a subject with a defective family history during an acute disease or during the various periods when the mental and physical powers are subject to the greatest strain.

My own belief is that the disease is due to an original developmental defect or inherent instability of the higher nervous mechanism, and that the physical symptoms suggesting auto-intoxication are the result of the imperfect formation of the central nervous system.

The views held by Dr. Lewis Bruce and others that the disease is of toxic origin and is due to bacterial invasion have not yet been confirmed, and I am not prepared to accept them in favour of the former theory. In the one case in which Lewis Bruce claims to have obtained a culture of a streptococcus from the blood, it is quite open to doubt whether this may not have been an accidental contamination of the flask, which is very difficult to avoid, even with the most rigid precautions, and confirmation of his results must come from other workers before the organism he isolated can be looked upon as a causal agent in the disease. Further, the recovery of an organism from the blood does not necessarily indicate that that organism is the cause of the disease. Organisms have been isolated from the circulating blood in other forms of insanity, for example in general paralysis of the insane, the pyogenic cocci, the bacillus coli communis and other organisms have been obtained, but these are not considered to be the causative agents of this disease. It is reasonable to suppose that during the various phases of any exhausting disease, there may be a transient invasion of the blood stream by various micro-organisms, and it is possible that this may be the case in dementia præcox, and that the blood serum of the patient may have the power of agglutinating the organism which has been recovered from the circulating blood.

The suggestion that the bacterial origin of dementia præcox can be substantiated by the presence of a leucocytosis has some grounds of merit, but may at the same time be fallacious, for it is to be remembered that several substances will cause some increase in the number of leucocytes in the blood, when injected into the blood stream or into the subcutaneous tissues. Even such fluids as normal saline when poured into the peritoneal

cavity will induce this to a marked degree. A leucocytosis, then, by itself is not sufficient evidence of bacterial invasion; it may be due to the production of some abnormal body as the result of an altered metabolism, or to the passage of substances from the alimentary tract into the blood; and these may or may not be produced by bacteria.

With regard to the changes produced in a rabbit by the injection of the streptococcus (for example, that of mental hebetude), surely the rabbit shows this particular feature as a normal characteristic.

Those who oppose Professor Kraepelin's nomenclature do so mainly on the following grounds:

1. That the term *dementia præcox* is inadmissible and unsuitable.
2. That only the katatonic form comes under his definition.
3. That *dementia præcox* does not exist.

With regard to the first objection, the term *dementia* is criticised on the ground that Professor Kraepelin himself admits to a small percentage of recoveries. Personally I doubt whether any true recovery does take place in this disease; at least my own limited experience inclines me to the opposite view. The term *præcox* (youthful, early or premature) is objected to on the ground that cases are reported as commencing between 35 to 40 years, which is past the period of adolescence and past the age at which the word *premature* is applicable. Now, *dementia* may set in at various age periods, and if this occurs prior to 70 years of age, it may be regarded as *premature* so far as the *dementia* is concerned, and the earlier the appearance the more hopeless the case, for the earlier onset points to the earlier dissolution of the cortical neurones. It is also possible that the few cases that are only noticed as commencing at the age of 35 to 40 years, may have presented mild and undiscovered symptoms at a much earlier period of life. Objections of this description are a mere quibble of words. If there is any justification for Kraepelin's views, then the title he has chosen should be retained until such time as a better one can be discovered.

There are others who can only comprehend the katatonic form as conforming to Kraepelin's description of the disease. It is to be remembered that Kraepelin himself has spent years of labour in evolving his ideas, and it is hardly probable that others can appreciate his observations to the full without prolonged and arduous study. To turn for a moment to other diseases, no one would deny that a person suffering from the cervical form of locomotor ataxia was not afflicted with that disease because he did not possess an ataxic gait, and no one would deny that a person was suffering

from Graves' disease because either the protrusion of the eyes or the enlargement of the thyroid was not apparent when all other symptoms pointed to that disease. So, too, I consider that no one is justified in denying that a particular case is one of dementia præcox because the katatonic state is not manifest when all other symptoms are apparent.

Those who deny the existence of dementia præcox as a definite entity would appear to forget that Kraepelin has not endeavoured to prove the existence of a new disease. He has throughout disclaimed any such intention, and has merely endeavoured to group together under a particular title certain symptoms and physical signs which appear to be common to a form of insanity commencing usually during adolescence and terminating in dementia. If under this particular heading he is able to include a number of types which previously have been classed under such vague terms as adolescent insanity, melancholia, stuporose melancholia and such like, he has earned the gratitude of many who are bewildered with the existing nomenclature of the disorders of the insane.

CONCLUSIONS.

In conclusion, I am of the opinion that (1) there exist certain cases of insanity with definite mental and physical symptoms to which Professor Kraepelin has given the name dementia præcox (for the purpose of advancing and simplifying scientific research); (2) that these cases commence usually about the period of adolescence, run a fairly regular course and never regain their proper mental faculties, although the progress of the disease can be arrested to a certain extent by early and careful treatment; (3) that hereditary influence plays a most important part in rendering the individual predisposed to mental breakdown at those periods when the stress of physical or mental development is liable to react upon the higher nervous centres; (4) that a proper appreciation of Professor Kraepelin's discussions will do much to promote a better understanding of these conditions and the early and appropriate treatment which is necessary for the welfare of those who are the victims of this form of insanity.

CASE 1.—G. W—, male. Age on admission, 19 years. Date of admission, May 21st, 1903. Single. Occupation, clerk in Board of Trade. First attack.

Family history.—Mother died of cancer of uterus. Mother's great grandfather died insane.

Family history of father.—Father's father was alcoholic and had rheumatism and eczema. Died at the age of 61 years, cause unknown. Father's mother was healthy; died at the age of 52 years.

Family.—(1) Father of patient, aged 53 years, healthy. (2) Sister, died young, pulmonary tuberculosis. (3) Brother, died young, diphtheria. (4) Brother, alive and healthy, aged 46 years. (5) Sister, alive and healthy, aged 44 years. (6) Brother, alive and healthy, aged 42 years; (7) Brother, aged 40 years. Chorea or tic. Twitchings of head since a child, otherwise healthy.

There were three children by this marriage. (1) Son, died aged 11 years, status epilepticus. Fits started when he was five years of age. (2) Daughter, aged 25 years, married, no children. (3) Son (patient).

Previous history (from father).—Patient was a full term child. Mother healthy during pregnancy, difficult labour. As a child was very sharp. Had measles. Went to private school when five years of age. Was extremely brilliant and took several prizes for drawing, painting, etc. Passed Cambridge Local Exams., taking prize for drawing. When sixteen years of age he was put in an auctioneer's office; this was not good enough for him, and he passed the examination as copyist at Trinity House and the Board of Trade. He always studied a lot, especially shorthand, but always avoided social life, taking life very seriously. Patient complained that he could not sleep, and he was heard walking about his room at night. He became very shy and lost his appetite. About this time his mother developed cancer. Patient sat and moped a lot, and took no interest in his work. At his office he would sit and do no work. He was sent into the country, where he walked all day and took but little food. For six weeks his condition remained the same. He was dull, stuporose, and lacked interest in his surroundings, and finally tried to jump in front of a train at the railway station.

Doctor at workhouse states: He is in a condition of semi-stupor. He has changed from a bright intelligent young man to a condition of mental feebleness. He has a fixed expression of the eyes, spasm of muscles of face, slowness of pulse, and coldness of extremities. Questions have to be repeated, then he answers in almost inaudible tones, repeating his answer several times. Gazes about in an absent-minded and indifferent manner, unless his attention is aroused.

Physical state on admission.—Ears, lobes attached. Palate, not examined, refuses to open his mouth. Hands and feet cyanosed. No emaciation. Fibrillary twitchings of muscles of face and hands. Pulse

80, irregular. Heart sounds, no murmur, second sound feeble. Lungs healthy. Pupils dilated, react to light and accommodation. Knee-jerks exaggerated. Often repeated contractions of muscles of forehead, pulling up his ears. Face mask-like, with occasional symmetrical twitching of facial muscles.

Mental condition on admission.—Patient lies in bed in supine position, Mask-like expression, no play of features when he talks. When questions are repeated he will answer in a monotonous almost inaudible tone. He has to be shouted at before he will answer. His answers are rational, but he repeats them. He takes no notice of his surroundings. Makes peculiar grimaces. Does nothing for himself. Defective habits. Saliva dribbles from mouth. He will stay in any position in which he may be placed, but there is a passive resistance to being moved. No rigidity. Constant stereotyped movements of the face, and he is constantly rubbing the thumbs against the first finger of both hands. Occasionally, for about twenty seconds, he turns pupils up under lids, or rapidly twitches both upper eyelids; this is repeated at intervals of a few minutes. At times he will sit for hours pulling his moustache with his left hand. He was turned on his side in bed, in which position he lay with his knees drawn up almost to his chin. In this position he was lifted on to the floor, and placed on the small of his back; he remained quite rigid for several minutes. He was then lifted on to his feet by the attendant and dressed. He passively resists all attempts to dress him. He is fed on sop with a spoon, and each meal has to be started, for if he is left with food before him he takes no notice. When pricked with a needle he gives an occasional grunt, but otherwise takes no notice. He ignores his mother and father when they visit him.

Progress of case: June 30th, 1903.—Remains in same state of anergic stupor, but has developed impulses. On occasions he will suddenly strike at anyone near him, immediately relapsing to his former state. He has attempted strangulation with his braces.

September 9th, 1903.—Remains much the same. He has gained in weight and takes quantities of nourishment. He is now quite rigid if any attempt is made to move him. Has to be carried about. He has many stereotyped movements, raises and lowers eyelids, moves ears and scalp backwards, constantly moving lips and tongue as if trying to remove a hair from the tongue. If a lighted cigarette or pipe is placed in his mouth he will smoke, but when they require relighting he takes no notice but merely stops smoking and sits with the cigarette or pipe in his mouth.

He never speaks, but at times he will give three or four loud screams, and occasionally suddenly strike those near him, immediately lapsing to his former state.

March 30th, 1904.—He is losing weight, is pale and anæmic, appetite poor. Never speaks. There is now no rigidity, but the stereotyped movements persist. Occasionally impulsive. He resists slightly if his limbs are moved, and when they are released he slowly replaces them.

March 30th, 1905.—For a year has been just the same, but now when impulsive he is violent and abusive for two to three minutes, then lapses into former state.

September 20th, 1907.—A little improved. He has had a note book and pencil given to him, and spends a lot of time drawing in it. He draws well from life and pictures he sees in the wards. He goes over the lines in his drawings time after time, and his hands move very slowly. If asked to write, he sits with pencil in hand and several times appears about to do so, but I never induced him to write. He now walks about when told to do so, but negativism is marked towards strangers, although he will do what the attendants ask him to do. He was taken over to the Laboratory to-day; he stood up in the room taking no notice of surroundings, with stereotyped movements of face and hands. He was told to sit down, but would not and resisted an effort made to force him to be seated. When told to stand up he would not, and when told to remain seated he immediately stood up. He displayed in turn automatic obedience and negativism, but did not speak. I then took his note book and pencil from him; he asked for them back. I said, "Why do you want them?" He replied, "Because father gave them to me." I opened the note book and he requested me not to look at it as it was private. I then placed it on the top of the door and told him he could have it; he at once walked to the door and reached up and took the book. I then gave the pencil to the attendant and told him to place it on the table in the next room. When I told the patient he could have it, he promptly walked down the passage into the room, took the pencil and came back. That night I took the pencil away from him. He argued with me for some time as to why he should have it, but would not talk on any other subject. I told him his pencil was in his coat in another room; he at once went and obtained the pencil and came back. He was at no time threatening or abusive, but quite polite and rational in his demands for his pencil. His comprehension appeared clear.

January, 1909.—Patient now shows signs of dementia. He is a case of

katatonic dementia præcox, with no signs of improvement since onset, but a **very gradual** progression to dementia.

CASE 2.—H. M—, male, single. Age on admission, 24. Admitted 21st March, 1900. Occupation, paper stainer. First attack.

Family history.—Not obtained.

Previous history.—Passed Standard V. Henglers Garden Board School. After leaving school he worked in a saw mill, but held several situations before admission to Asylum. He states that he was discharged from some for carelessness and from others because trade was bad. He admits drinking “four ale” in excess, and that he used to get drunk. He attended Great Ormond Street Hospital till 5 years old for rickets.

Doctor at workhouse states that the patient was brought to him in a state of excitement, having been found, it was asserted, attempting to hang himself. He soon lapsed into a state of extreme mental depression and would not answer questions, or did so in such an undertone as to be almost inaudible. In this condition he has remained for some days, showing no disposition to occupy himself in any way.

The lunatic attendant at workhouse states that he has seen the patient repeatedly performing acts of masturbation.

Physical state on admission.—Anæmic; extremities cyanosed; pulse 80, irregular; small; constipated; palate low and broad; lungs and heart normal; forehead narrow and frontal bones thickened; tibiæ curved from rickets; generally ill developed; height 4 ft. 10 ins.; weight 7 stone.

Mental state.—He sits about all day and does nothing. He never initiates any movements, and has to be dressed. Questions have to be repeated several times before he answers, and then he speaks in a slow and monotonous undertone. He never speaks unless addressed. He is dull, apathetic, and unemotional. There is slight mental confusion. His memory is fair. There is reluctance to taking food.

September 3rd, 1900.—He has become stuporose and resistive and has to be fed by the tube. He resists senselessly all attempts to move him, and he will remain for hours in any position in which he is placed. He takes no apparent interest in anything going on around him. He passes his urine and fæces in bed or in his clothes. Everything has to be done for him.

May 20th, 1902.—With the exception of a few weeks at a time, he has been fed by the tube since September, 1900, and has remained in the same state. During the last few months he has become fatter, and brighter mentally. He has lost all resistance, but is still dull and apathetic. He

now dresses himself, takes his food, is clean, and does a little work on the farm. At times, however, he stops working and remains in a fixed attitude till started again. Negativism has gone, but he is quite unemotional and lacks initiative.

April, 1903.—He has remained in an improved state during the past year, but has suddenly relapsed into a condition of anergic stupor. He has to be fed by the tube and is again in a state of *flexibilitas cerea* and negativism. He remains sitting or standing in any position he is placed with all his muscles tense and resistive. He looks vacantly in front of him. His face is expressionless, and he takes no notice when addressed. He grimaces, puckers his forehead and moves his ears, and at times rubs his hands together, or his head with his right hand for hours.

March 30th, 1903.—During the past year he has remained in the same condition. Electric baths have been given (ten minutes) three times a week for two months, but with no mental change. However, he now takes his food and is becoming fatter.

December, 1907.—He has remained in practically the same state; at times, however, he has to be fed by the nasal tube. He has been having cold baths each morning. At the present time he is much brighter, but sits most of the day in the ward apparently taking little notice of what is going on around. He is always fidgeting, frowning or rubbing his hands on face, etc., or together, or rubbing his fingers with his hands or pulling at his coat with both hands. He gets up when called, dresses himself, is clean, and has a certain amount of pride in his appearance. He speaks aloud and asks for what he wants. When addressed he smiles and answers readily. His face now has a lot of expression, and his memory is fair. He remembers being fed by the tube, when and who fed him, etc., and his negativism, and states he wanted to take his food and wanted to do what he was told, but *could not start*. He says that he always made an effort but it was no good, and that he understood all that was said and done around him when he was in a state of *flexibilitas cerea*. He is cheerful and does a little automatic work, such as sweeping and scrubbing. When asked if he would like to go home, he smiles and says "I wouldn't mind"; he gives the same answer when asked if he would like some tobacco, or a shilling, or to see his mother. He was given three pieces of paper the same size with A on 1, B on 2, and C on 3. He was told to fold them up and to give A to me, B to an attendant, and to put C in his pocket. These directions were given quickly and were not repeated. He carried them out correctly. He knows the value of coins and can do addition

and subtraction sums. He writes and spells well both copying and from dictation.

January, 1909.—The symptoms remaining now are his dulness and apathy, his lack of initiative and a few stereotyped movements, and he has remained in this state for the past two years.

He is a case that could go to the care of friends as *improved*, had he the friends to take him, but it would be impossible for him to earn his living.

CASE 3.—W. A. D—, male, single. Age on admission 25 years. Admitted February 28th, 1908. Occupation, soap maker. First attack.

Family history.—Not obtained.

Previous history.—He was educated at Bromley Road Board School. He left school at the age of thirteen when he was in the 4th standard. He was quick but lazy. He was employed at the Central London Railway and at Cook's Soap Works, and at both places he was a steady worker.

Doctor at workhouse states that he refused to speak and to move himself. He held himself in a rigid position.

Physical state on admission.—Teeth clean, carious, a few stumps; tongue red and clean; palate high and narrow; ears deformed, large and flat; forehead narrow and low. Chest symmetrical, well developed; muscular; no emaciation; lungs healthy. Respirations 14, three or four shallow then one deep inspiration; heart irregular, sounds are normal; pulse 80, irregular in time and force. Pupils equal, react to light and accommodation. Heart becomes very irregular if a loud noise is made near him. Fibrillary twitchings of facial muscles. Constipation. Adenoids. Cyanosis of feet and hands. Sensation, heat, cold, and pain, no reaction. Height 5 ft. 11 in.; weight 12 st. 7 lb.

Mental state.—Patient lies in bed on his left side curled up; he takes no notice of any remark addressed to him, although spoken loudly and repeated six times. He takes no apparent notice of anything. When an attempt is made to raise his head he passively resists. When his limbs are moved there is rigidity, and he remains in whatever position he is placed. His eyes are closed, and if any attempt is made to open them he tightly shuts the lids. When the upper lid is raised he turns the eyeball right up out of sight. He was placed in bed on his back and both arms were lifted straight up from the bed; he remained in this position for twenty minutes and then put them down on the bed. There is complete loss of all spontaneous movements. Face is mask-like and expressionless, except when frowning. Every few minutes there is a contraction of

muscles of forehead, at times accompanied by a slight whining noise. When food is placed in his mouth he swallows it. When placed on stool he passes urine and fæces; he is not defective in his habits, but would be if he were not placed on the stool at intervals. There is mutism.

The patient was laid flat on the bed and his right leg was raised six inches; it remained in this position for 1 minute 18 seconds. The leg was at once raised again and he held it in position 1 minute 5 seconds, and on raising again for subsequent periods of 35 seconds, 45 seconds, 25 seconds, 15 seconds, and afterwards for periods of 5 to 10 seconds, showing the rapidity with which muscular fatigue comes on.

March 1st, 1908.—Patient has not spoken since admission and there is no change in his condition. He has no reaction to heat, cold, or pain; a needle can be placed in him anywhere, and even if it is left there he takes no notice. Since admission he has laughed on two occasions when something humorous took place in his presence, although apparently he was not taking any notice at all.

May 10th, 1908.—This evening when he was being put to bed he suddenly screamed incoherently and then called the attendant by name. I went down and saw him; he spoke quite rationally, and his memory was exceedingly good for all past events both before and during his state of katatonia, of which there were no signs present. He told me the names of the doctors that had seen him, the names of the other patients in the ward, and all that had happened around him since admission, and his comprehension was quite clear. He stated that he had desired to talk, but had been unable to do so.

January, 1909.—He remained apparently quite rational for three weeks during which time he worked well and read a great deal. He then rapidly developed signs of dementia. He is at present dull, unemotional, and lacks all interest in his surroundings and all power of initiative. He dresses himself when told to do so, slowly and mechanically. He does not move all day, and will sit quietly for hours where he is placed. He will answer simple questions at times, but usually takes no notice.

He is a case of dementia præcox (katatonia) with rapid progression to dementia.

CASE 4.—E. G. R—, female, single. Age on admission 19 years. Admitted 29th May, 1906. Occupation, fancy box maker. First attack.

Family history.—Father's mother died aged 74 years; always healthy. Father's father died aged 45; diabetes. Mother's mother died aged 32; cause of death, parturition. Mother's father died aged 69; senile decay.

Mother's sister, aged 40; lupus of face. Mother's sister, aged 44; healthy. Mother's brother, aged 40; died at sea. Mother's brother, aged 17; died paralysis, duration 14 days. Father has five brothers, all healthy.

Family.—(1) Miscarriage; (2) Girl, aged 26 years, healthy; (3) Girl, aged 24 years, healthy; (4) Boy, aged 20, healthy; (5) Twins; Patient. Four miscarriages followed birth of patient.

Previous history.—Patient was a full term child, a twin. She was late in walking—suffered from diarrhœa—scarlet fever, aged nine. At school from 4½ to 13 years of age, left when in the 6th standard, after passing top examination. She always did well. She started box work and was a very steady and good worker. Always suffered from anæmia, and treatment for years did but little good. Three weeks before admission she developed the idea that she had done something wrong, that she owed money and that people were coming after her.

Doctor at workhouse states that patient refused to take food and would not speak.

Physical state on admission.—Ears, lobes attached; palate, broad and low; teeth poor, several carious; gums inflamed; saliva dribbles from mouth. Very anæmic but well nourished. Constipation. Heart sounds normal; pulse 60, very small, difficult to feel at wrist, regular. Skin dry and cold; no secretion of sweat. Urine 1·020, acid, phosphates. Hands and feet cold and cyanosed; hair dry. Face, fixed expression, mask-like, absolutely no play of features; eyes, winking very frequent, more so than normal; pupils dilated, equal, react readily to light and accommodation; Babinski's sign normal. Lungs healthy. Chest and limbs well formed.

Mental state.—Patient lies in bed in supine position with head and shoulders raised from the pillow; she makes no effort of any kind to get comfortable. Her expression is mask-like, and she remains quite still, taking apparently no notice of her surroundings. When an attempt is made to move her limbs there is passive resistance. She will do a few acts after being told several times. She very slowly put out her tongue about ¼ inch. A question "How old are you?" was repeated several times; she answered in an almost inaudible tone, and the same occurred when asked her name. She writes her name and address, and yes and no in answer to questions. She holds the pencil just as it is put in her hand, making no attempt to grip it correctly. She writes very slowly and deliberately, a good hand with spelling correct. She will not answer any questions referring to the last three weeks. She was made to sit up in

bed in order to write, in which position she remained ; there is absolutely no voluntary movement. When her right arm was raised above her head and released, she held it there ; after three minutes the left arm was raised, the right arm came down slowly with jerky movements to the bed, and the left arm was held up. After ten minutes the right arm was raised and the left arm came down to the bed. There is passive resistance against all attempts to move her limbs. She is lifted from her bed in the morning and dressed, and is fed with a spoon, a nurse holding her hand and conveying the spoon to her mouth. After this has been repeated a few times she proceeds to feed herself, continuing until the sop is finished. When placed in a chair she sits there all day, never moving or taking any apparent notice of what is going on around. She is walked round the airing court between two nurses. She takes no notice of her mother, and does not alter in the least during her visits. She at times answers a few questions, and these answers show no mental confusion or dementia.

October, 1906.—Patient has remained in the same state since admission, but during the last few weeks she has improved. She now converses and takes a little interest in her surroundings, is clean in her habits and looks after herself. Her memory is good, but she is still dull.

March, 1907.—Patient's mother took her out on trial as she had been in same state as noted above for some months. She relapsed after being out four weeks, and when brought back was in the same state as when she was first admitted.

January, 1908.—Patient has remained in same state since last note.

January, 1909.—The patient is still in Asylum and remains in a state of stupor. She never speaks and has to be fed with a spoon, and is defective in her habits.

There is in this case a family history of neuroses, diabetes, tuberculosis, and paralysis. I am unable to obtain information regarding the nature of the paralysis. The mother had four miscarriages after patient was born, showing that at this time procreation in the parent was enfeebled. The fact that the patient was a twin would also account for her having a defective stability of the neurons. At school she showed signs of good mental development. After usual onset she developed signs of katatonia. There has been no improvement in this case. Her progression to dementia is very slow.

CASE 5.—M. F—, female, single. Age on admission twenty years. Admitted November 14th, 1906. Dressmaker. First attack.

Family history.—Father's father died at fifty ; tuberculosis. Father's brother, Colney Hatch Asylum. Father's sister died at thirty-four ; tuberculosis. Of this sister a son died at eleven years of age, two daughters at twelve and two years respectively, and another child died in infancy, all from tuberculosis. Mother's mother, Colney Hatch Asylum. Mother's cousin, Colney Hatch Asylum. Father has asthma, drinks heavily, and his wife states that he is mentally defective. Mother aged forty-nine years, healthy. The mother has three sisters and one brother all married and healthy. One sister has a son aged twelve years who has tuberculosis.

Family.—1. Son, died in Colney Hatch Asylum, aged twenty-four, tuberculosis. 2. Son, alive, aged twenty-six years, healthy. 3. Daughter. Patient. 4. Daughter, aged nineteen years. Has been in Temperance Hospital for "mental breakdown" for six months and has improved a little. 5. Son, alive, aged eighteen years, healthy. 6. Daughter, alive, aged seventeen years, healthy. 7. Daughter, alive, aged fifteen years, has tuberculosis. 8. Son, died, aged two years, from tuberculosis. "The doctor said he was an imbecile."

Previous history.—Patient was a full term child. She was bright at school and left at the age of thirteen, when in the top standard. She then became a dressmaker and was always a hard and steady worker. A few months before she was taken to the infirmary she became reticent and solitary in her habits. She spent a lot of time "brooding," and one day she suddenly threatened to "knife" the family. Doctor at the workhouse states :—"She states she held sexual intercourse in a workroom filled with people, with a man named Rev. Barber who was dressed in woman's clothes. She is absolutely positive that this is so, and has taken medicine to prevent consequences. The mother states that patient has become very idle and sleepless of late."

Physical state on admission.—Nutrition good. Palate, broad and low ; teeth clean, a few carious. Constipation. Heart regular ; pulse 60, small. Lungs healthy. Skin dry ; hands and feet cyanosed. Pupils dilated and equal, react to light and to accommodation. Knee-jerks equal and exaggerated. Chest and limbs well developed. Catamenia irregular for some months ; anæmic.

Mental state.—The onset was acute. The patient was in a state of excitement after prodromal period for two months, during which she was sleepless, reserved and brooding. She is now excited and talkative ; her conversation is incoherent, full of long sentences, and unusual and strange

words. She is extremely erotic, and has had many mysterious ideas. She states that she is under the influence of Mr. Barber, that he has seduced her, and that she is a very important woman. She must go into the world and do what he tells her. She decorates her dress in an extraordinary manner with anything she can obtain; at the same time, however, she is untidy and slovenly. She strikes strange and peculiar attitudes, and walks in a bizarre manner. She appears to do these things without any consideration of her surroundings, and takes no notice of anyone. At times she is impulsive, but the impulses are quite senseless. She has to be dressed, and everything has to be done for her. She has no apparent pleasure in the visits of her relatives or in receiving presents from them.

January 2nd, 1907.—She has now become much quieter, but is dull, reticent, and lacks all interest in her surroundings. She is idle, childish and at times laughs senselessly. She is still incoherent in her conversation, writing, and actions.

January 9th, 1909.—She is now demented, and has lost her impulses. She dresses herself, is clean in her habits, and eats her food, but beyond this she does nothing. She can answer a few simple questions, but usually, when addressed, she does not answer.

I consider this to be a case of dementia præcox hebephrenia; after an acute onset of excitement and hallucinations she remained for two years in a peculiar condition, best described as a state of incoherence in words, writing, action, and behaviour. During this time she has been slowly progressing to dementia.

CASE 6.—A. D—, single; age on admission, 23 years. Admitted February 5th, 1907. Male, hawker; first attack.

Family history.—Father died seven years ago of phthisis, was alcoholic; mother dead some years, cause unknown; father's uncle, alcoholic.

Previous history.—From brother, who is a clerk in Civil Service. Patient went to St. Matthew's National School when aged four, and left at the age of fourteen when in the 6th standard (highest standard, 7th). He was dull at school, "easy-going and easily imposed on." He obtained first prize for writing and for drawing. When he left school he became an errand boy, and brother lost sight of him till he came here.

Patient states that he earned his living drawing portraits in public houses, and drank a lot of beer. At one time he was employed by the 'Star,' and sketched for them. The 'Star' have sent him presents of

drawing materials since he came here, in appreciation of his services. He states that he got into bad company, that all his money was taken from him each week, leaving him just enough to live on, and that his friends thought him an idiot.

Doctor at workhouse states : " He is acutely melancholic and deluded. He says he is dead and that his stomach is falling out, that he has ruined his constitution by leading a wrong life."

Physical state on admission.—Head circumference, 22 in.; skull square, protuberances over frontal and occipital bones; eyes close set; ears, lobes attached and small; palate high and very narrow; teeth irregular and decayed; pupils equal, react to light and accommodation; knee-jerks equal, exaggerated.

Mental state.—He lies in bed in a supine position. Has a dull, set, vacant expression, and takes no notice of what is going on around. When addressed he does not answer, but stares straight in front of him. He does nothing for himself, and after he has been dressed he sits where he is placed with his lips apart and saliva dribbling from his mouth. He lacks all initiative and is quite unemotional. He eats any food that is given to him, and is defective in his habits.

February 28th, 1907.—Patient remains in the same state of stuper and *flexibilitas cerea*, with negativism. He has a habit of moving his head slowly from side to side. He apparently now watches all that goes on around him, and has a good appreciative perception of rational conditions, but he is in an absolutely subemotional state. He passes his motions and urine under him.

March 30th, 1907.—He now does a little for himself, helps when he is dressed, but still has marked impairment of volition.

September 14th, 1907.—There has been a gradual improvement in this patient during the last few months, but he remains demented. He dresses himself, takes his food well, attends to Nature's calls, and asks for what he wants. He does no work in the ward, but picks hair when a bundle is placed in front of him. He often sketches other patients, and his work is good. He talks freely, repeats questions put to him, and frequently repeats portions of his answers or words. His memory is fair.

"How old are you?" "Twenty-four."

"What day were you born?" "12th September, 1883."

"How long have you been here?" "Six months."

"Yes?" "Yes."

"What day is this?" "About the 16th."

"Of what?" "September. Yes, to-day is September, Yes."

"What year?" "1907."

"What have you done during your life?" "I have had a funny career, but I have never had trouble with the police. Of course, I am a bit silly. I am a sketcher, of course not an expert, but a gifted person. I came here of my own accord. I am sane, but did not want to give the public trouble."

"Will you write your name on this paper?" He sits looking at paper, with pencil in hand, and flourishes it as if about to start, but does not. After question was repeated three times he says, "Shall I write my grandfather's name? Shall I write my own name? I was a great swimmer when a boy—Shall I write my name?" He then wrote his grandfather's name, slowly and deliberately, at times lifting pencil and flourishing it a lot over the paper. He then wrote his grandfather's address—"Neal St., Long Acre." Then he wrote his own name, and then: "My grandfather was a good family, Long Acre, yes—Long Acre—of course. I'm not insane. I get my living sketching in public houses."

He mutters to himself and says he hears funny voices and that it is an "illusion." He has delusions of persecution, stating that people pull his bed from under him, and pull his clothes off him, but he adds, "I don't mind—no—no—it does not matter." There is no forcible complaint demanding justice as in paranoia. There is a good deal of dementia, complete dulness of emotions, and loss of association of ideas.

January, 1909.—Patient is still in the Asylum. He daily does a little work, hair picking, and this he performs in a mechanical manner. He is dull, apathetic, and lacks initiative.

There is a history of amentia, an ament of high order. There is also a history of drink and stress at puberty. I look upon him as a case of dementia præcox (katatonia) gradually progressing to dementia.

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The Pathology of Dementia Præcox, especially in relation to the Circulatory Changes.*

By G. H. RAE GIBSON, M.D., M.R.C.P.E.

THE physical condition of patients suffering from dementia præcox is so characteristic and so different from that in other types of insanity that it has always been regarded as one of the outstanding features of this disease.

It is difficult to attract the attention of the patient either by speaking or by a sudden noise, and when he had been induced to respond to any advances the mental reaction is very slow. It takes sometimes minutes to obtain an answer to the simplest question, yet apparently the patient is making an effort to reply. Movements, when they are performed, are slow, ill-timed, and frequently misdirected. The patient is apathetic, and has frequently an appearance of stupor, which at times is accompanied with a certain facility, so that he is easily made to smile. This sluggish, torpid state is not confined to the mental faculties, for we see present all the features eminently characteristic of low physical condition. The signs of a low state of vitality are seen not only in the expressionless face and expressionless hand, but also in the shallow breathing, the feeble pulse, the cold extremities, and the various gastric and intestinal derangements which are so constantly noted in these patients.

It was these physical abnormalities, and more especially the circulatory defects, which first suggested an examination into the condition of the blood-pressure. I was advised by Dr. Mott to estimate the arterial tension in these cases, in order to see whether any circulatory defect was present which might be associated with the mental and physical states above alluded to.

At Claybury, Colney Hatch, and Morningside Asylums I estimated the blood-pressures in over a hundred cases of dementia præcox, and have

* Abstract of a Thesis for the Degree of M.D. at the University of Edinburgh.

further, by way of controls, taken readings in other types of insanity and in sane people, some of whom were in good health and others suffering from various bodily diseases.

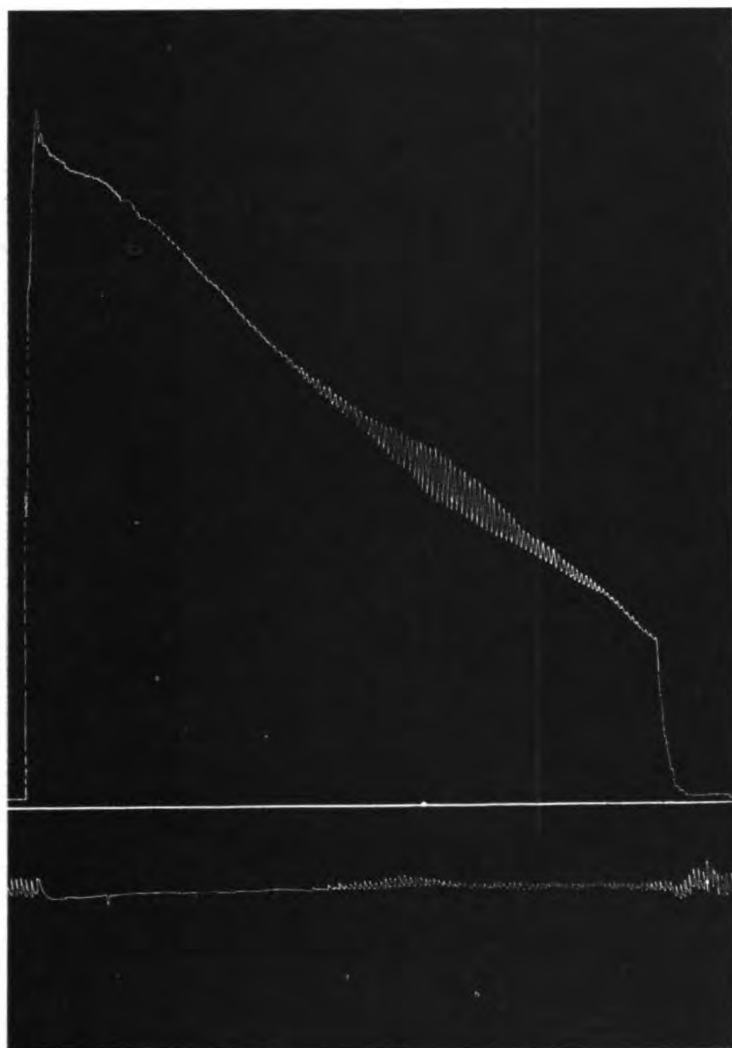


FIG. 1.—Tracing from a normal male aged between 20 and 30. Systolic pressure 135. Diastolic pressure 100. Normal systolic pressure. Diastolic pressure rather high.

At Colney Hatch the readings were obtained in the presence of Dr. Mott and Dr. Gilfillan; at Claybury Dr. Harper-Smith very kindly gave me his assistance; and at Morningside I was helped by Dr. Babington and Dr. Simpson.



FIG. 2.—Tracing from the pulse of a patient with dementia præcox. Katatonia, female, aged 25 years. Systolic pressure 88. Diastolic pressure 74. (*Gibson's sphygmomanometer.*)

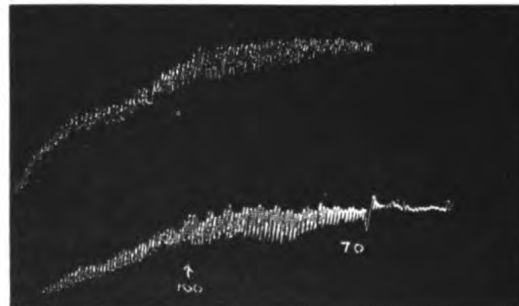


FIG. 3.—Same patient. Systolic pressure 95. Diastolic pressure 70. Very low blood-pressure. Systolic and diastolic pressures have a very small interval between them. (*Erlanger's sphygmomanometer.*)

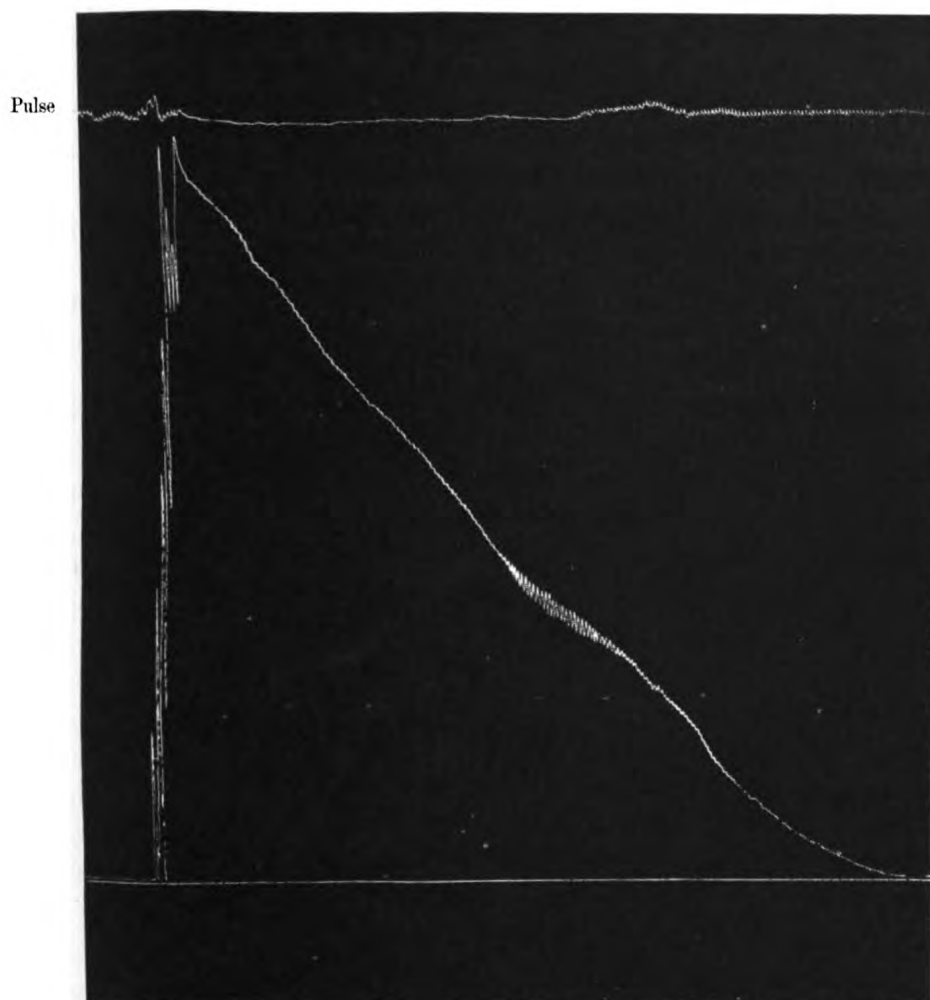


FIG. 4.—Tracing from the pulse of a male patient with dementia praecox. Paranoia, aged 45 years. Systolic murmur 94. Diastolic pressure 82. Low blood-pressure. Small interval between systolic and diastolic pressures. (*Gibson's sphygmomanometer.*)



FIG. 5.—Tracings taken from the same patient on a different day with Erlanger's sphygmomanometer. Systolic pressure 108. Diastolic pressure 70. (*Erlanger's sphygmomanometer.*)

For the sake of accuracy, and for a comparison of results, three instruments were employed—Gibson's and Erlanger's graphic sphygmomanometers, and the Riva Rocci sphygmomanometer.

In every case readings were taken with the Riva Rocci, and the other two instruments were used in selected cases by way of illustration.

I have divided the results obtained according to sex, with the following sub-divisions, as they belong to the three types of the disease—katatonia, paranoia, and hebephrenia.

The other types of mental disease which I have examined are epilepsy, general paralysis, and congenital imbecility.

The normal blood-pressure in a healthy adult, between twenty and thirty years of age, may be considered to be 130 mm. of mercury, as obtained from readings with the Riva Rocci sphygmomanometer. This agrees almost exactly with the readings obtained by Gibson's and Erlanger's graphic sphygmomanometer.

Several writers, among whom are Janeway, Hill, Doleschal, and Jarotzey, place the normal blood-pressure in the healthy adult between 100 and 130 mm. of mercury, but the majority estimate it at rather a higher level. Some of the writers who are in favour of this higher reading for the normal arterial pressure are Hayaski, Hensen, Thayer, Potain, von Basch, Gibson, and Russell. The average for women is slightly lower than for men, and is probably 125 mm. of mercury.

It will be noticed that in cases of disease of the circulatory system, as in aortic and mitral disease and in aneurysm, as long as the lesion is compensated and the general bodily health remains in good condition, the arterial pressure is well maintained, and may even be higher than normal. This is very well shown in the tracings taken from people suffering from cardiac disease. In one case of aortic disease the pressure was as high as 190 mm. Hg., and in no case was it below 130. In the cases of mitral disease the lowest reading obtained was 120, which was in a case of incompetence with poor compensation. In aneurysm the tracings were, if anything, rather higher than normal.

The tracings of the cases of anæmia showed a very different state of affairs; the arterial tension was low, being especially so in a man with secondary anæmia.

In the cases of general paralysis the average results in the cases of seven men whose average age was forty-five, was 138; and 126 for eight women with an average age of forty-four. This shows that in general paralysis there is apparently no marked deviation from the normal, as it

is practically the height of blood-pressure commonly found in people at that age.

In epilepsy I was rather handicapped by not being able to obtain many female cases. The results obtained are rather below normal. Isolated cases, however, gave readings which show little deviation from that of health. The men, whose average age was thirty-six, had an average pressure of 120, and the two women I examined, one a case of epilepsy with ovarian affection, show an average of 124.

The tracings and readings taken from cases of congenital imbecility are interesting from the fact that they show low arterial tension. Six male congenital imbeciles, of an average age of twenty-one, had an average systolic pressure of 115; and four women, of an average of thirty-four, had a mean pressure of 109.

In the cases of dementia praecox two facts are noticeable: In the first place, the average of the readings is low; and, in the second place, there is a very frequent occurrence of readings below 100 mm. of mercury.

The katatonic males, of an average age of twenty-eight, had an average systolic blood-pressure of 113 mm. Four of these cases, however, showed readings of below 100 mm. Eighteen females with katatonia, of an average age of twenty-eight, had an average pressure of 111 mm. Six had pressures of below 100 mm.

Thirteen males, of the hebephrenic type of dementia praecox, of an average age of thirty, had an average pressure of 118 mm.; and fourteen females, of an average age of twenty-seven, had an average pressure of 114 mm. In each set of cases there were two with blood pressures of less than 100 mm.

The average arterial tension was higher among the paranoiac cases than in the other two types of the disease. This was especially so among the female patients, of whom I examined thirty cases.

Sixteen male patients with dementia paranoidis, of an average age of thirty-five, had an average pressure of 113 mm. In two instances the tension was below 100. The female patients, of an average age of forty, had a blood pressure of 125 mm. The higher pressure in this group of cases may be partly accounted for by the fact that the average age of these patients was higher than that in the other two varieties of the disease.

Blood-Pressure in Twelve Cases of Epilepsy.

Males.	B.P.	Age.	Females.	B.P.	Age.
1. J. C— . . .	105	34	1. Mrs. R— . . .	115	45
2. A. W— . . .	155	60	2. Mrs. M— . . .	133	34
3. J. R— . . .	105	29			
4. R. B— . . .	110	25	Average B.P. . .	124	
5. W. L— . . .	110	43	„ Age . . .	39.5	
6. J. R— . . .	145	53			
7. R. T— . . .	130	26			
8. T. S— . . .	123	36			
9. J. J— . . .	105	35			
10. G. D— . . .	114	25			
Average B.P. . .	120				
„ Age . . .	36				

Blood-Pressure in Fifteen Cases of General Paralysis.

Males.	B.P.	Age.	Females.	B.P.	Age.
1. D. J— . . .	140	35	1. Mrs. F— . . .	119	38
2. J. R— . . .	150	58	2. Mrs. C— . . .	115	50
3. R. F— . . .	163	34	3. Mrs. A— . . .	116	50
4. W. M— . . .	127	32	4. Mrs. S— . . .	150	45
5. W. B— . . .	123	40	5. Mrs. A— . . .	145	70
6. J. W— . . .	123	58	6. Mrs. S— . . .	127	28
7. J. C— . . .	141	64	7. Mrs. L— . . .	110	32
			8. Mrs. B— . . .	128	43
Average B.P. . .	138		Average B.P. . .	126	
„ Age . . .	45		„ Age . . .	44.5	

Blood-Pressure in Ten Cases of Congenital Imbecility.

Males.	B.P.	Age.	Females.	B.P.	Age.
1. H. R— . . .	105	23	1. J. Y— . . .	100	24
2. J. B— . . .	108	20	2. M. D— . . .	120	60
3. W. S— . . .	119	19	3. M. K— . . .	99	30
4. G. B— . . .	125	19	4. L. D— . . .	117	24
5. G. D— . . .	114	25			
6. G. T— . . .	118	19	Average B.P. . .	109	
			„ Age . . .	34.5	
Average B.P. . .	115				
„ Age . . .	21				

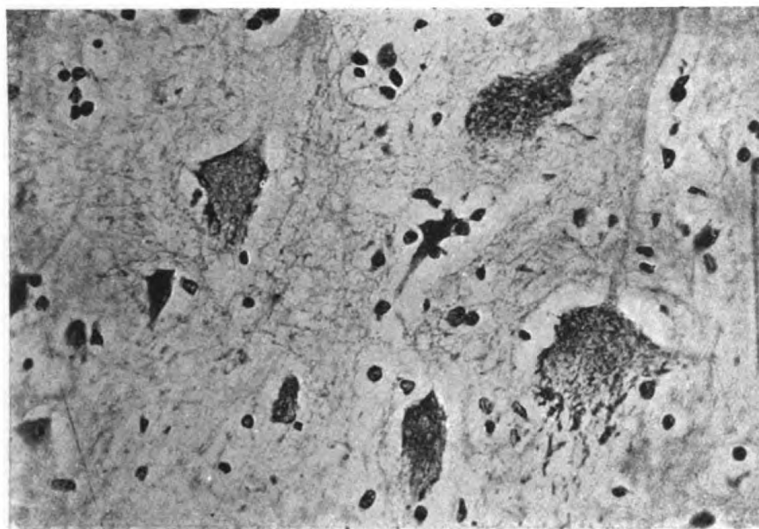


FIG. 7.—Photo-micrograph of a section of top of ascending frontal convolution: dementia praecox with katatonic stupor, showing several large Betz cells in which there is a disappearance of the Nissl pattern; the nucleus is not seen probably owing to its eccentric position. There are also groups of proliferated neuroglia nuclei. Magnification 330.

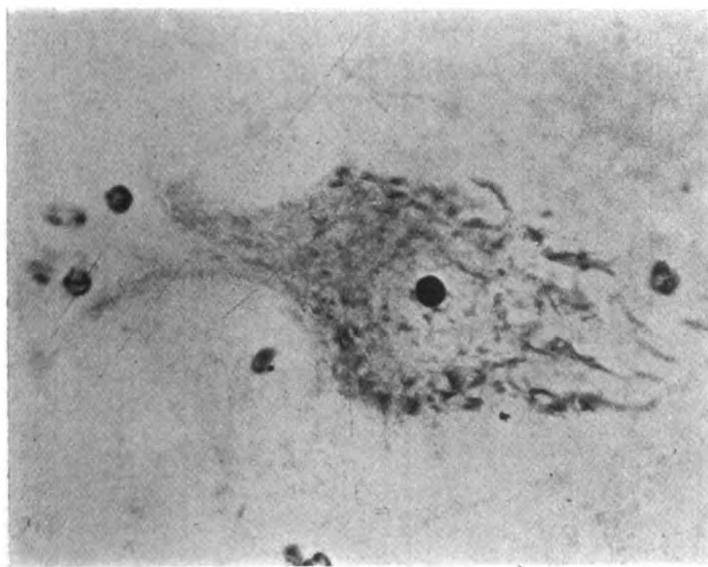


FIG. 6.—Betz cell, showing swelling and chromatolysis. Dementia praecox. Magnification 750.

Blood-Pressure in Thirty-three Cases of Katatonia.

Males.	B.P.	Age.	Females.	B.P.	Age.
1. M. B—	97	21	1. H. E—	89	25
2. S. A—	125	32	2. J. C—	145	39
3. W. M—	124	27	3. R. B—	88	24
4. F. E—	87	19	4. E. L—	98	27
5. W. W—	85	23	5. M. B—	135	22
6. J. R—	97	31	6. W. K—	117	29
7. G. L—	103	28	7. H. P—	125	31
8. T. L—	110	21	8. C. M—	127	28
9. A. H—	128	43	9. E. M—	87	18
10. C. R—	122	27	10. A. P—	100	25
11. T. M—	103	25	11. F. C—	107	30
12. H. J—	146	37	12. E. C—	87	33
13. H. H—	140	41	13. M. F—	117	29
14. M. H—	116	25	14. L. G—	120	41
15. T. E—	112	19	15. S. W—	97	20
			16. E. T—	120	23
			17. L. M—	120	27
			18. A. S—	114	26
Average B. P.	113		Average B.P.	111	
„ Age	28		„ Age	28	

Blood-Pressure in Forty-six Cases of Paranoia.

Males.	B.P.	Age.	Females.	B.P.	Age.
1. F. L—	100	26	1. A. C—	145	62
2. G. B—	90	33	2. S. K—	102	67
3. J. A—	100	29	3. F. M—	138	36
4. T. A—	90	27	4. E. B—	112	38
5. G. W—	100	25	5. M. H—	150	55
6. G. N—	128	36	6. L. P—	107	29
7. M. H—	126	34	7. M. A—	135	46
8. B. C—	120	31	8. M. S—	135	51
9. B. W—	97	27	9. J. H—	140	39
10. S. P—	149	60	10. G. P—	115	29
11. L. P—	111	48	11. A. D—	105	31
12. P. G—	129	37	12. E. S—	95	32
13. S. A—	147	49	13. A. S—	115	33
14. N. G—	117	41	14. L. E—	130	40
15. M. N—	109	36	15. M. G—	130	36
16. J. A—	107	31	16. A. R—	135	37
			17. R. P—	110	33
			18. K. F—	239	46
			19. B. M—	113	41
			20. S. L—	135	42
			21. A. S—	145	46
			22. B. L—	120	33
			23. P. J—	133	38
			24. S. S—	136	50
			25. A. M—	123	37
			26. M. F—	109	42
			27. H. E—	137	41
			28. J. P—	141	55
			29. F. W—	136	38
			30. P. A—	117	33
Average B.P.	113		Average B.P.	125	
„ Age	35		„ Age	40	

Blood-Pressure in Twenty-seven Cases of Hebephrenia.

Males.	B.P.	Age.	Females.	B.P.	Age.
1. H. C—	119	27	1. R. M—	148	39
2. G. S—	125	25	2. M. C—	139	35
3. W. M—	133	33	3. R. R—	145	40
4. J. C—	88	30	4. C. E—	100	22
5. E. D—	97	28	5. M. F—	115	27
6. J. B—	153	49	6. F. A—	100	25
7. W. C—	130	31	7. E. J—	100	24
8. W. L—	110	22	8. H. D—	114	19
9. F. B—	150	43	9. W. G—	93	27
10. D. C—	100	27	10. E. B—	88	22
11. H. G—	102	26	11. H. K—	113	30
12. W. P—	115	24	12. M. K—	112	31
13. C. S—	117	31	13. F. W—	123	34
			14. E. H—	101	19
Average B.P.	118		Average B.P.	114	
" Age	30		" Age	27	

Table of Blood-Pressures.

	MALES.		FEMALES.	
	Average B.P.	Average age.	Average B.P.	Average age.
Dementia præcox katatonia	113	28	111	28
" " hebephrenia	118	30	114	27
" " paranoia	113	35	125	40
Epilepsy	120	36	123	39.5
General paralysis	138	45	126	44.5
Congenital imbecility	115	21	109	34.5

From the above tables it is evident that in dementia præcox there is, generally speaking, a low arterial tension, indicating a circulatory failure which may be associated with many of the physical manifestations characteristic of the disease, viz. cold extremities, chilblains, blue fingers, feeble pulse, and a general low bodily condition.

What part, if any, does this circulatory condition play in the production of the mental symptoms? To answer this question I have investigated the histology of the brains of four cases of dementia præcox, with the view of ascertaining if there are changes in the structure of the cortex and sub-cortical tissues which could be associated with defective circulation.

While working in the Laboratory at Claybury, four brains were examined microscopically. Three of these were the brains of patients who had died in Claybury Asylum, and one was that of a patient who died

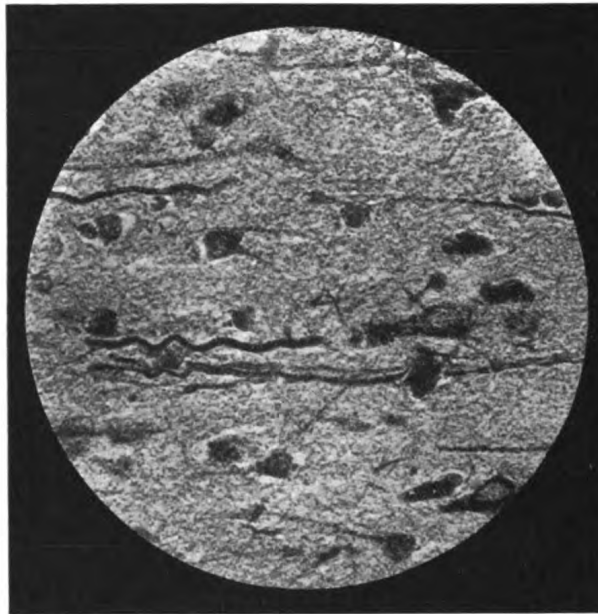


FIG. 8.—Section of top of ascending frontal convolution : dementia præcox. Cajal stain, showing twisting of the apical processes of pyramidal cells. Magnification 460.

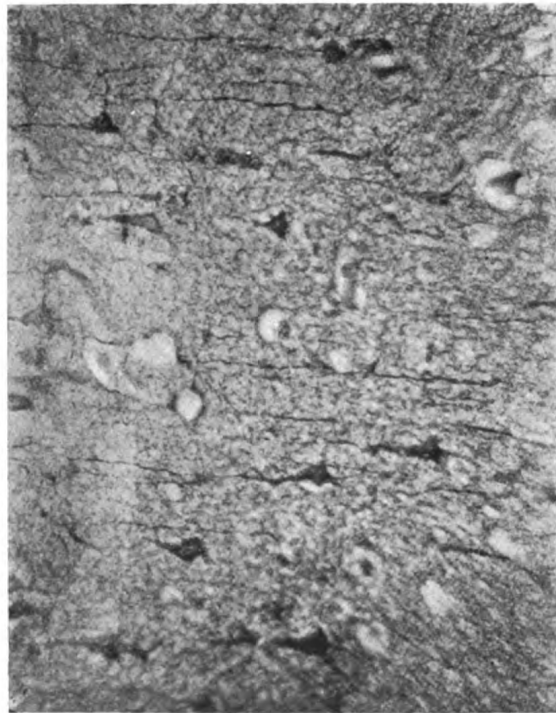


FIG. 9.—Dementia præcox, showing twisting of apical processes of pyramidal cells. Magnification 360.

in Bexley Asylum, for whose history and post-mortem notes I am indebted to Dr. Stansfield.

HISTOLOGICAL CHANGES IN THE BRAIN.

The changes I detected in greater or less degree in each of these four brains are in the main similar to the appearances described by various authors. These appearances may be regarded as commonly occurring in dementia præcox, yet cannot be considered as pathognomonic of the disease as they occur in other conditions.

Before, however, we can correlate these histological changes with the symptoms manifested during life, it is necessary to exclude conditions which may be coincident or accidental. The most important of these is post-mortem change. In the brains under discussion, this may, I think, be eliminated. The three patients who died at Claybury Asylum were placed in the cold-chamber at the Laboratory immediately after death, and at the post-mortem examination I placed the brains at once into 5 per cent. formol. In the case of the patient who died at Bexley Asylum, the post-mortem was performed at a time after death which would exclude the probability of post-mortem changes; the brain was placed in 5 per cent. formol.

For the microscopical examination, the same procedure was adopted in each of the four brains under investigation. Sections were cut from various parts of the frontal, parietal, temporal and occipital lobes, the optic thalamus, the pons, medulla and cerebellum. Portions of the caudate and lenticular nuclei were also examined. The right and left hemispheres were chosen indifferently, and in two of the brains sections were taken from both hemispheres.

There was no sign of wasting in three of the brains. In the one case where it occurred, it was confined to the region of the superior and ascending frontal regions. The cerebral convolutions were well formed and were conventional in type; there was no thickening of the membranes and no sign of granulation in the fourth ventricle.

Sections were cut, of 5μ in thickness, from paraffin blocks and stained with hæmatoxylin and eosin, hæmatoxylin and Van Gieson and polychrome blue, and by Nissl methods; also by the Heidenhain eosin method for neuroglia. Portions of the tissue were also prepared for staining by the Cajal neurofibril and the Weigert Pal methods.

MICROSCOPICAL CHANGES.

The most marked changes were in the ascending and the superior frontal convolutions. The rest of the frontal region was affected, but not to such an extent. The posterior and inferior portions of the brain showed much less abnormality than the anterior and superior. In the inferior parietal and temporo-sphenoidal convolutions and in the occipital lobe few changes were to be found. The alterations affected principally the deeper layers, and the psychomotor cells of Betz and the large pyramids were markedly affected, as was also the polymorph layer (figs. 6 and 7). Slight abnormalities could, however, be detected throughout the entire depth of the cerebral cortex, but near the periphery they were less marked.

The normal arrangements of the cells into the columns of Meynert was disturbed, and the general appearance was rather irregular.

In the cells themselves, various alterations in size, shape, and staining reactions were visible. Some of the cells were swollen, and their sides were more rounded, so that they appeared more circular than normally.

Some cells were faintly stained, others were small and shrivelled, with broken and interrupted cytoplasm and without any sign of nuclei. These different abnormal cells were not found in groups, or confined especially to any one part, but frequently were seen lying side by side, so that it was quite common to observe a normal cell lying beside an affected one.

Besides the faintness of staining which many of the cells presented, there was a homogeneous aspect, so that in sections stained by polychrome blue the cells presented a uniform dull purple staining.

Changes were also seen in the nucleus which had undergone alteration and assumed various shapes. In some instances it was slightly distended, in others it was greatly enlarged, while occasionally it was eccentric and at times extruded.

Extrusion of the nucleus was not found very frequently, but when it occurred it was accompanied by various manifestations indicative of cell disintegration and destruction.

Twisting of the apical processes of the cells giving them a cork-screw shaped appearance was frequently observed; and the dendrons were deficient in number or apparently broken off or atrophied (figs. 8 and 9). This cork-screw appearance Dr. Mott ascribes to the atrophy of the dendrites, which keep the cell in position and make taut the apical process; consequently when these atrophy or disappear the apical process



PLATE I. CELLS FROM CORTEX. *TEMENTIA PRÆCOX*.
Polychrome stain. Magnification high 480, low 160.

is no longer held in a tense straight vertical position towards the surface and therefore becomes lax and twisted.

Chromolytic changes are usually observed, for instead of the mosaic pattern presented by the Nissl bodies, a fine dust, scattered irregularly through the cell, may be seen, or the basophil substance is in clumps, or seen running in long threads. Accompanying this change and usually preceding it is a deficiency or absence of chromophilous material in the dendrons (*vide* Plate).

There was in addition, generally speaking, a proliferation and hyperplasia of the neuroglia cells, especially in the deeper layers of the cortex.

There was in these sections none of the signs seen in sections from cases of general paralysis, no sign of perivascular cell infiltration or of vascular proliferation. In one of the brains, that of a man who had been completely demented for some years, there was a considerable deposit of pigment appearing through the brain substance and also in the cells themselves.

In addition, many of the cells showed signs of vacuolation, many vacuoles occurring at times in one cell.

It was noticeable, further, that the supporting cell substance was less dense than usual; there was a general appearance of thinning and vacuolation.

In one of the brains, in the case of a man who had shown marked stereotyped movements during life, the Betz cells were the most affected—an interesting fact, in view of the psychomotor phenomena this patient exhibited during life.

Changes similar to those which I have found have already been described by several writers. Dunton noted a slight cell change which was distributed over the whole surface of the brain, but most marked in its appearance in the region of the first frontal convolution.

Dr. Stewart, investigating a case in the Claybury Laboratory, found chromolytic changes with eccentric nuclei, which was most marked in the larger and middle layer of pyramids, but also present in the smaller layer.

Dr. Mott refers to four cases with marked dementia, where there were marked evidences of degenerative changes in the pyramidal cells.

Various other investigators, among whom are Alzheimer, De Buck and Deroubaix, have noted similar changes in the polymorph layer and in the layer of the larger pyramids.

The abnormality in the Purkinje cells which Lannois and Paviot have described, I was unable to find.

Dr. Mott, in the Croonian Lectures, 1900, has described two sets of changes which occur in experimental anæmia which had been artificially induced in animals by Dr. Leonard Hill. Firstly, when two carotid and two vertebral arteries have been ligatured in dogs which subsequently recovered completely. Secondly, when a subclavian was tied instead of one of the vertebrals, so that a sufficient collateral circulation could not be restored soon enough and the animal died at a period varying from one quarter to twenty-four hours. In the first set of experiments the dogs were demented and paretic, remaining for some days in a state similar to those dogs in which Goltz removed the cerebral hemispheres. They were restless, irritable, stupid, standing with a fixed gaze and their legs spread out.

Dr. Mott, on examination of the brains of these dogs, found various changes in the nerve cells. The cells were swollen up, with bulging sides. The nuclei were likewise increased in size and were at times eccentric. Alterations were further noted in the chromophilous material, the Nissl bodies had disappeared and their place was replaced by a fine dust: in addition to these changes there were other cells which were irregular in outline, with broken cell-walls and extruded nuclei. Examination of the spinal cord ten days after ligature of the arteries showed only a few degenerated fibres in the crossed pyramidal tracts. Dr. Mott was therefore of opinion that the universal changes noticed in the cortical cells were of a functional character. This observation accords with the fact that the animal recovers all its cerebral functions completely and in a fortnight after the operation, as far as can be judged, behaves like a normal dog.

In the case of the second series of experiments, in which ligation of the arteries supplying the brain was performed in such a manner that a collateral circulation was not established, quite different appearances were noticed.

The cortical changes showed a shrivelling rather than a swelling of the cells, and the cell bodies showed more signs of fragmentation with the extrusion of the nuclei and twisting or rupture of the terminal processes. The perivascular spaces were greatly dilated and scattered; through the protoplasm of the cell was a fine dust of chromophilous particles. The cells and their processes stained a uniform pink or purple, and there was none of the differentiation and brilliant colouring met with normally in sections stained by means of the methylene blue and safranine, or of polychrome blue.

These cell changes have been described by Dr. Mott: "The whole cell stains uniformly, but not with a brilliant coloration. If a double stain has been used, for example methyl blue and saffranine, the whole cell may be stained a uniform dull purple, the processes, as well as the body of the cell, having a homogeneous instead of a differentiated reaction to the dyes. One animal, a monkey, which became demented and paretic after ligation of both carotids and one vertebral, was killed on the fifth day and the following changes were found. The nerve-cells and their processes were stained uniformly a diffuse dull purple and were readily discerned on account of the dilatation of the lymph space in which the neurone lies; scattered through the protoplasm of the cells was a fine dust of coloured particles; the special processes of the cells were either destroyed, or twisted like corkscrews; in many the dendrites had disappeared, but in some the axis cylinder could be traced with unusual distinctness, probably due to some swelling. Many of the cells were swollen up and others were shrunken. Some could be seen with phagocytes sticking to them and devouring the dead cells."

As Dr. Mott has shown, "every neurone has a specific energy of its own, and its functional capacity and durability depend upon three factors:—

1. The inherent vital energy to maintain biotonic equilibrium.
2. The condition of the circumambient medium which provides the necessary chemical substances for functional activity and repair of waste.
3. A capacity of the neurone for storage of energy whereby it is enabled to meet stress under conditions in which immediate repair of waste is rendered difficult or impossible."

From the study of the family histories of cases of dementia praecox, and the frequent occurrence of a family hereditary predisposition, it is evident that in these patients the brain-cells have probably insufficient vital energy to maintain biotonic equilibrium.

These faulty hereditary tendencies make the nerve-cell more liable to suffer under adverse circumstances than would be the case in persons who were without family predisposition to nervous and mental troubles.

Verworn, in his recent work, has determined that the spinal centres were capable of discharging without receiving oxygen or nutritive material. From this it is evident that the spinal motor neurones possessed a store of latent energy which, under certain circumstances, such as various stimuli, "could be converted into potential energy, independently of the circulating blood." When there is failure of repair of waste, there

ensues loss of function which has been termed *exhaustion paralysis*. Dr. Mott has pointed out that this may be due to "failure of the oxygen storage, or in exceptional experimental cases, to failure of organic material." The ganglion contains reserve stores of oxygen and of organic material. The former are more readily exhausted than the latter. When a nervous centre is exhausted, it is on account of the using-up of the reserve oxygen substance and the neurone is, as it were, asphyxiated.

When we consider the fact that many of these patients are the heritors of neuropathic destinies, it is not unlikely that the inherent defect lies not only in the possession of insufficient vital energy to maintain biotonic equilibrium, but also in the oxygen storage capacity of the cells. The result of this is that any conditions limiting or destroying the supply of oxygen to the nerve-cells will have much more marked results than in normal tissues.

Several factors may unite together to cause conditions unfavourable to the stability of the nerve cell. The equilibrium of the cell elements may be disturbed by various toxins, bacterial or auto or cyto-toxins, and if this occurs in normal cells, it is much more probable that it will take place in those which are inherently defective.

Many of these patients are subject to tuberculous disease, and, as Dr. Mott has pointed out, the tuberculous toxin may be an important causative or exciting agent in these changes.

The similarity of the changes noted in dementia præcox to those found in the brains of animals as a result of experimental anæmia points, however, to other factors which may have an important share in bringing about these changes.

It has already been shown that these patients suffer from a grave circulatory defect. The feeble pulse, the various digestive disturbances, and the cold extremities which are so frequently met with in these patients, bear witness to the fact that the various components regulating the blood flow are not functioning properly.

The post-mortem manifestations exhibited by these patients confirm the appearances so frequently noticed in life. Their hearts are frequently dilated, and the ventricular walls flabby and dilated.

It is, however, not only the *vis a tergo* or force pump action of the heart which is affected in these patients. Persons suffering from dementia præcox are shallow breathers; during inspiration they exhibit very slight chest expansion, so that the *vis a fronte* or sucking mechanism of the heart is also markedly impaired.

These various conditions, coupled with the fact that these patients lead a sedentary existence, all tend to cause a low state of arterial tension.

Any lowered state in the circulatory tension will be felt in the brain as much as in the various organs of the body from the anatomical arrangements which govern the cerebral mechanism. The anatomical arrangement of the veins of the brain, and more especially of the longitudinal sinus, with its various tributaries, is such that any change in the general circulation will show its effect in this region.

Dr. Mott has demonstrated the importance of this arrangement of the cerebral circulation in the determination of neurotic destruction in general paralysis.

"The veins of the brain have no muscular fibres in their coats; they consist of an adventitia, lined by an endothelium, and the large veins which run into the longitudinal sinus often run for an inch or so in the substance of the dura mater before opening into the sinus in a direction opposite to that of the current. The chordæ Willisii in the sinus and in these sinusoidal veins would facilitate stagnation of the blood, and this would occur much more frequently than it does were it not for the fact that the great anastomotic vein is connected by a large vein with the lateral sinus, so that obstruction in the longitudinal sinus finds a relief by this connection."

In his paper on the etiology and pathology of general paralysis, Dr. Mott has shown that the thickening and opacity of the pia arachnoid membranes correspond with those parts of the brain which are drained by the superior longitudinal sinus.

The portions of the brain in which the maximum changes were found in dementia præcox were mainly in the anterior portions of the hemispheres. The mesial surface of the frontal lobe, the top of the temporo-sphenoidal and the anterior two-thirds of the upper and outer surfaces of the hemispheres were most affected, and the appearances were most marked in the upper part of the ascending frontal and the superior frontal convolutions.

These are the portions of the brain drained by the superior longitudinal sinus.

These alterations are not mainly biophysical, as shown by dropsical aspect of the cells, due to the absorption of cerebro-spinal fluid and the chromatolysis; biochemical changes have also taken place, as shown by the shrunken appearance of some of the cells and the change in the staining reactions.

It is probable that oxygen is diffused through the whole nerve cell in a state of chemical combination ; therefore it is not difficult to understand how these biochemical changes are brought about by circulatory factors interfering with the blood flow through the brain.

It is probable that, in the early stages of dementia præcox, the change is purely a physical one, brought about by various factors tending to lower the general health. In this stage, the nerve cells are deteriorated and in a state of low vitality. As the disease progresses, there is an accumulation of the products of destructive metabolism, and with it degeneration of the cell elements, which goes on to a state of actual destruction.

How far the actions of various toxins aid in the production of these changes is difficult to say. It is commonly said that various forms of mental disease are a result of intoxications, but so far we are ignorant of their cause and of their chemical properties. It is not unlikely, however, that some form of intoxication is an important factor in the production of the changes seen in this disease, in conjunction with the circulatory defect and the mechanical arrangements of the cerebral blood supply.

In any case, we see the formation of a vicious circle, which any pathological process tends to accelerate, in which impaired nutrition, the shallow breathing, and the low state of the arterial tension all participate.

TREATMENT.

The treatment which I have adopted at Morningside is directed towards stimulation of the circulation, so as to cause an increase in the blood-pressure, not only in the general systemic circulation, but also in the vessels of the brain.

The patients were induced to take cold baths and were well rubbed down afterwards, and they were sent out for rather more vigorous walks than is customary with asylum patients. They were further directed to practise breathing exercises. Their food was carefully attended to and extra diet, along with milk, custards, and maltine and cod-liver oil, given with a view to improving the general health of the patients. The drugs employed were mainly cardiac tonics and those which seemed to yield the most satisfactory results were digitalis, strophanthus, nux vomica, caffeine and adrenaline. Of these, the results apparently obtained with 7½ minims of tincture of digitalis and 10 minims of tincture of nux vomica were the best. These drugs were administered three times a day for a fortnight as

a general rule, and then an interval of a week was allowed to elapse. In the case of the patient M. G., the nurses were emphatically of the opinion that the patient was better while she was taking the medicine and not so well during the intervals.

Of the eleven cases in which the treatment was adopted, two have been discharged, and two are shortly going out: one recovered completely mentally, but unfortunately developed phthisis and died in the institution; one recovered from her katatonic condition, but has since turned into a state of what might be termed criminal lunacy, and five have shown practically no lasting change, though even in the most unsuccessful cases certain slight changes, which can, I think, be ascribed to the treatment, were noticed.

The general health was, in every case, attended to for a period of at least three weeks before any drugs were administered.

The cases were all of the katatonic variety, with one exception. The first change noticed in the patients was an increased restlessness, which showed itself in various ways. One patient, who had been apathetic and apparently demented for months, suddenly attempted to throw herself out of the window, and patients who had previously been quiet and well-behaved, taking no interest in the surroundings, became irritable and quarrelsome. They all professed dislike to their medicine, and in several cases it was necessary to administer it forcibly. In one case, C. B., the treatment was successful in little more than two months, but in the other cases the average period was from three to six months.

The following is a brief account of the clinical histories of the cases on which the treatment was tried:

E. L—, aged 20 years, female, single; domestic servant. Admitted to the Royal Edinburgh Asylum on the 16th October, 1909. Her mother had been insane and was also at Morningside. There was nothing in the previous history of the patient of any moment; she had been of average intelligence at school and showed a certain ability, especially in arithmetic.

When admitted was mentally enfeebled, with a poor memory and no proper idea of her surroundings. When I first saw her, at the commencement of November, she exhibited all the signs of katatonia; she never spoke; had to be fed; was untidy in her habits and personal appearance, and sat still listlessly and apathetically. Her arms and legs could be placed in any position, and when so left, remained for several moments; she also showed a slight tendency to Schnautzkramf. Her general health was

fairly good, but her blood-pressure was so low that the pulse was almost imperceptible at the wrist, and with the graphic sphygmomanometer no pulsation could be obtained. With the Riva Rocci, the blood-pressure was estimated at 98. Her hands were very cold and her fingers covered with chilblains; her ankles and feet were swollen and oedematous. She was treated with digitalis; with digitalis and nux vomica; with strophanthus; hypodermic injections of strychnine, but with very little result. Certainly she was more restless and spoke occasionally, but except for the fact that her blood-pressure at times was 108 and once rose to 112, there was very little change. When she was treated with adrenaline, however, she began to improve and is at the present moment progressing steadily. She takes her meals and talks, and except for a slight facility, is almost in a normal mental state. The adrenaline has been discontinued, but she still continues to get small doses of digitalis and will very shortly be discharged.

M. G—, female, aged 28 years, single; lady's companion. Admitted to the Royal Edinburgh Asylum on the 11th October, 1909.

An uncle and a sister were insane. She had always led a reasonable, quiet, steady life, and had had no illnesses beyond the ordinary complaints of childhood. She had an attack of influenza two years before admission, and, six weeks later, was thrown out of a motor car and her chin was rather badly damaged. Six months before admission, she attempted suicide by strangulation. When she came to us she was very depressed; thought that she had been poisoned, and that she was dead; was refusing her food and under the impression that she had done grievous bodily harm to her relations. Mentally, except for the fact that her memory was very bad, there was only slight impairment; she talked readily and coherently, but had auditory hallucinations, to which she responded. Her physical health was very poor; she was thin and anæmic, and her heart was very irregular and her knee jerks greatly exaggerated. When I saw her first, in the beginning of November, she was very depressed, sitting for hours without speaking and slightly katatonic. Her heart was irregular and her pulse very feeble, and her blood-pressure 112 mm. of mercury. Her general health was carefully attended to, and the anæmia treated by putting the patient to bed and giving her milk and Bland's pills, and at the end of six weeks her condition had improved so much that it was deemed expedient to start treatment with cardiac tonics. She expressed great dislike to the drugs, and on several occasions it was necessary to administer them by means of the nasal tube. She was under treatment

for altogether seven months, and the most satisfactory results were obtained with adrenaline, administered by the mouth. This, as with the other cardiac tonics, was administered over periods of a fortnight, with weekly intervals. During the intervals of treatment, the patient was undoubtedly not so bright as while the drug was being administered. She eventually improved so considerably as to be discharged recovered.

G. K—, female, aged 27 years, single; housekeeper. Admitted to the Royal Edinburgh Asylum on the 23rd August, 1909.

For some months previous to her admission had been dull and listless, untidy in her appearance and personal habits, neglecting her work, and sleeping badly. She had gradually sunk into a condition of apathy, and for some weeks had not spoken or taken any interest in her surroundings. As she had been refusing food, it was necessary to remove her to an institution. She had once attempted suicide by precipitation. There was the history of an older sister who had been insane, suffering from what appears to have been systematised delusional insanity; the father also was weak-minded. On admission she was wringing her hands, spoke seldom, only to complain of the great sins which she had committed, and showed slight signs of katatonia. Her physical health was weak; she was very thin and anæmic, but her heart and lungs were healthy. When I saw her first, in the beginning of November, she presented all the signs of katatonia, she had to be tube fed, and she was an excellent example of Schnautzkramf. Her eyes were tightly shut, and she sat for hours in one position with her head bowed. From the middle of December, 1909, to the commencement of April, 1910, she was treated with digitalis and nuxvomica, and during the fortnights while the drugs were administered she was resistive and impulsive; but, at the end of three and a half months' treatment, there was very little change in her mental condition. On the 10th April she suddenly showed a marked improvement; sat up straight, talked sensibly, took her food, and conversed fairly rationally; said she was sorry for the trouble she had caused, and inquired after her relations. Shortly after she developed a cough and a swinging temperature, and though her mental condition continued to improve, she died on the 8th May of acute miliary tuberculosis.

C. A. B—, female, aged 24 years, single, was admitted to the Royal Edinburgh Asylum, on the 20th October, 1909, with a history that for some time past she had lost all interest in her work, had been troubled with sleeplessness, and had had no appetite for her food. She attempted to commit suicide on at least one occasion by strangulation, and had

demanding to be given a razor with which to cut her throat. She was occasionally violent, and for seven weeks prior to her admission had been regarded and treated as insane.

When admitted to the asylum she was at first very depressed and her memory was impaired. She suffered from various delusions—amongst others, that she was guilty of unpardonable sins; that her food was poisoned, and that everybody was conspiring against her.

Her appearance was decidedly depressed; she sat still, with her head bowed, saying nothing.

Her heart and lungs were both healthy; but her hands were cold and covered with chilblains, and her blood-pressure was 106.

When I first saw her, in the beginning of November, she was very slightly katatonic. She was refusing her food, and had to be fed on several occasions. Her appearance was that of complete depression, and she looked exceedingly unhealthy. Her general health was attended to for three weeks, after which it was thought that she was ready to be treated with various cardiac tonics. She at first was very resistive when the drugs were administered, and complained bitterly about the bad taste. Altogether she was under treatment for about two months and a half, during which time she was treated almost entirely with digitalis and tincture of nux vomica. At the end of this time she had entirely recovered, and remained so for the next three months when she was discharged. I have heard from her several times since, and she still remains in the best of health.

C. P—, female, aged 15 years, admitted to the Royal Edinburgh, Asylum on the 8th of January, 1910; a mill-worker.

About three months previous to admission she had had a great fright, as when she was alone in the house a drunken man had suddenly entered the room in which she was asleep. The August before, she had had an accident and fallen on her head and had been insensible for some three days, during which she had what was described as a fit. She apparently had recovered from this completely, and remained perfectly well until four weeks before she was admitted. She then completely altered in her conduct; refused to work; her conduct was extraordinary in many ways; she threatened suicide and almost entirely refused to speak to anybody. She was sent to the Royal Infirmary, where she became completely katatonic, and remained there for four weeks.

When she was admitted to the Royal Edinburgh Asylum she was an extremely marked case of katatonia, taking no interest in her

surroundings, answering none of the questions which were put to her, showing no signs of emotion, and with no expression on her face. As her physical health appeared excellent she was at once treated with cardiac tonics—first with digitalis, and later on with strophanthus. On the 23rd of February she began to speak; but for some time previously her movements had been much less rigid. By the middle of March she was speaking with comparative facility, and by the beginning of April she was able to work in the laundry and was in every way apparently normal. Since then she has shown no further indications of katatonia, but her general character has undergone a complete change. She is now what might be termed a criminal type of lunatic. She is defiant in her manner; attacks the nurses; fights with the other patients; is perpetually breaking windows, and refuses to do anything that she is asked. But, mentally, she appears to be quite active, as she writes long letters to her relatives and is able to talk intelligently and even cleverly.

B. D—, aged 20 years, single. Admitted to the Royal Edinburgh Asylum on the 16th March, 1909, with the history that six months previous to admission she became quiet, silent, unable to sleep, and had no appetite for her food.

When admitted she was morose, melancholic, dejected; answered questions very slowly and with apparent difficulty; contented herself with monosyllabic answers. She was perpetually asking to get home, and at times crying. She had hallucinations of hearing, and said that she heard her sisters and relatives talking to her. She was very anæmic, but otherwise in fair bodily health. Her general appearance was both dirty and untidy.

She was still in the institution when I saw her in the beginning of November in the same year, and during her residence had made no improvement whatsoever. She was occasionally impulsive, smashing glass and trying to escape, occasionally striking the nurses. After her general health had been attended to in the manner described above, she was treated with adrenaline. This was continued for two periods of a fortnight, with a week's interval, and, as there was apparently no change, she was treated with digitalis, at first alone, and then along with *nux vomica*. The treatment was continued at intervals for nearly five months, during which time her blood-pressure rose from 102 to 104. Under treatment she was at first exceedingly restless, occasionally noisy and excited; but gradually this passed off and, instead of spending most of the day asleep, or sitting still in the corner, she requested to be allowed to work. She

is still continuing to improve, and will probably be discharged in the course of a few weeks.

The five cases in which the treatment yielded no lasting results were those of patients who had all been resident for more than two years in the institution, and two had been inmates for over five years. In these cases I consider that the dementia had been so firmly established that actual degeneration and destruction had taken place in the brain cells, so that no improvement could be expected. I do not insert their histories, as they were typical cases of dementia præcox, four exhibiting katatonic symptoms, while one was a case of the hebephrenic variety.

In conclusion, I should like to express my thanks to the Laboratory Committee of the London County Council for the assistance accorded to me and the hospitality enjoyed by me at Claybury.

I take this opportunity of thanking Dr. Mott for his unfailing kindness and consideration; his advice was invaluable, and his constant encouragement most stimulating.

Dr. G. M. Robertson, of Morningside, kindly permitted me to practise the treatment on various cases under his care, and to him my heartiest thanks are due.

CONCLUSIONS.

1. That the changes in the nervous elements in dementia præcox are at first functional, and that in the later stages of the disease actual degeneration and destruction takes place.

2. During the early stages of the disease, temporary recovery is possible. Recovery during the later stages of the disease cannot occur.

3. Though recovery does take place during the early stages of the disease, it is only temporary, as all cases tend to relapse.

4. Bad hereditary tendencies are important predisposing causes to the onset of dementia præcox.

5. Circulatory disturbances, by impeding the supply of oxygen to brain tissues predisposed to disease, are important exciting factors in the onset of dementia præcox.

6. Toxins, whether microbial-toxins, auto-toxins, or cyto-toxins, probably play a certain part in the causation of this disease.

7. That the mental state is largely dependent on the physical and especially the circulatory condition, and that in early cases any improvement in the two latter is bound to show its effect in the former.

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On the Cortex of the Auditory Centre, the Insula, and Broca's Convolution in a Case of Deaf-mutism.

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THE following researches concern the brain of a male deaf-mute, whose internal ear has been investigated by Mr. Sidney Scott, M.S.* They were performed in the Pathological Laboratory of the London County Asylums, and I would here express my indebtedness to the Pathological Sub-Committee of the London County Council for permission to work in the laboratory. To the director of the laboratory, Dr. F. W. Mott, F.R.S., I owe great thanks for the material and for many valuable suggestions.

MATERIAL AND METHODS.

The material consisted in the brain of a man named S.H—, who suffered from an ear disease when six months old, and became deaf and dumb in consequence. Besides that he was an epileptic, and probably a congenital imbecile. He understood what was said to him by finger demonstration. He died at the age of thirty-two of acute lobar pneumonia and cardiac failure in Claybury Asylum. Post-mortem: the weight of the brain appeared to be 1,470 grammes.

Two normal brains from female adults whose hearing during life was normal were obtained from Charing Cross Hospital; these served as controls. I will indicate them with the letters A and B. Brain B was in every respect a normal one, but brain A was obtained from a chronic alcoholic, who, however, did not present any psychic manifestations like Korsakoff's disease.

The three brains were preserved in formalin. In order to cut the cortex everywhere as vertically as possible, the parts to be studied, *i.e.*, the gyri of Heschl, the first temporal gyrus, the insula and Broca's convolution were first drawn, and subsequently divided into pieces, each

* Mr. Scott's results will be communicated in the 'Proceedings of the Royal Society of Medicine.'

not more than 2 c.m. in length. These, after dehydrating in alcohol, were embedded in paraffin at 52° C., and cut by means of the Rocker microtome into a series of sections of 10 μ . In the series the number of sections was counted, and every hundredth section was taken out, stained with Nissl-Seifen-Methylenblau from Grüber and studied. If necessary more sections were treated in the same way. It will be obvious that by knowing the thickness and number of sections the precise place of a section should be indicated in a drawing of the brain made when it was still intact.

THE HESCHL-GYRUS AND THE FIRST TEMPORAL-GYRUS.

Only the left temporal lobe of the deaf-mute was studied by me, the right one being used for other purposes.

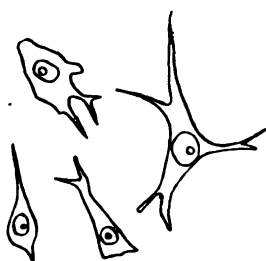


FIG. 1.—Outlines of four giant cells. Camera drawings. 110 Mag.



FIG. 2.—Outlines of four large supra-granular pyramids. Camera drawings. 110 Mag.

The outer appearance was quite normal (Pl. I, fig. 1). The two gyri transversi or Heschl gyri were not separated. This may also occur in normal cases, and accidentally it was true in the normal brain B (Pl. I, fig. 2).

The structure of the normal cortex in the transverse and first temporal gyri has been described among others by Campbell ('05), Brodmann ('09), and Marinesco and Goldstein ('10), who discuss also the preceding literature.

Campbell ('05) discriminates three temporal types of cortex, two of which are of more importance to us. The first is confined to the gyri of Heschl. It is chiefly distinguished by the existence of scattered, large cells in the supra-granular pyramidal layer (or third layer of Brodmann) called giant cells by Campbell. These giant cells occasionally lie within or even below the granular layer. Their form varies, at times being

pyramidal, at other times stellate, their processes are stout (Fig. 1), and so they differ in shape from the large pyramidal cells in the same layer (Fig. 2).

The second type occupying the first temporal gyrus and the anterior part of the gyrus transversus, resembles much the first one. Compared with the type of the Heschl-gyrus there are more large pyramidal cells in the supra-granular layer, but the number of the giant cells is considerably reduced.

Brodmann ('09), who gives no particulars about the structures of the different areas is able to recognize two areas on the Heschl-gyrus indicated by the numbers 41 and 42. The area of the first temporal gyrus agreeing sufficiently with that of Campbell is area 22. Besides, Brodmann notices an area 52 being a transition from the Heschl-gyrus to the insula.

Marinesco and Goldstein ('10) having examined the cortex of the temporal lobe in a considerable number of normal cases, agree in several respects with Campbell. They too see a striking difference between the cortex of the Heschl-gyrus and area 22 in the number of the so-called giant cells, this being less in area 22. Marinesco and Goldstein raise objections against the term "giant cells," because the giant cells of the temporal lobe are not comparable with those of the area *giganto-pyramidalis* or motor area. This is quite true; but bearing this in mind, I prefer the term "giant cells" to the not very characteristic term "large cells," which is used by Marinesco and Goldstein. Marinesco and Goldstein have found it difficult to find a difference between Brodman's areas 41 and 42. According to them the "giant cells" are more numerous in 42 than in 41.

The description of Marinesco and Goldstein was in nearly every point applicable to the normal brain B, which I studied. I observed the Heschl-gyrus to be chiefly occupied by an area characterised by a number of giant cells often lying in small groups, in the third or supragranular pyramidal layer (Pl. II., fig. 1). As I cannot find any reason to divide this area into two, 41 and 42, I shall indicate it as (41 + 42) (Pl. I., fig. 2). In this respect I agree with Campbell, and also with Marinesco and Goldstein; but not with Brodmann ('09), who, however, himself calls the areas 41 and 42 very similar to one another in tectonical respects (Brodmann '07).

The form of the giant cells, which were as Campbell describes, rarely lying in (Pl. II., fig. 2) or even immediately below the granular layer, is often not quite pyramidal, but stellate or spindle-shaped. By this character and their larger dimensions they differ from the large pyramids

FIG. 1.

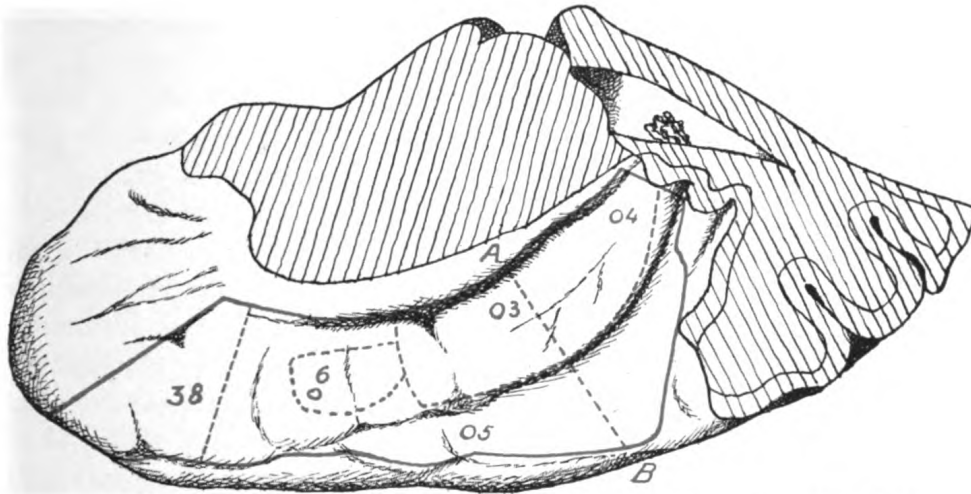


FIG. 1.—Left temporal lobe of a male deaf mute. Natural size. The red line indicates the portion cut and studied. The red dotted lines indicate the limits of the areas of different structures. 38 = area 38 of Brodmann. (3) — (6) spots where the drawings of Plate II were taken.

FIG. 2.

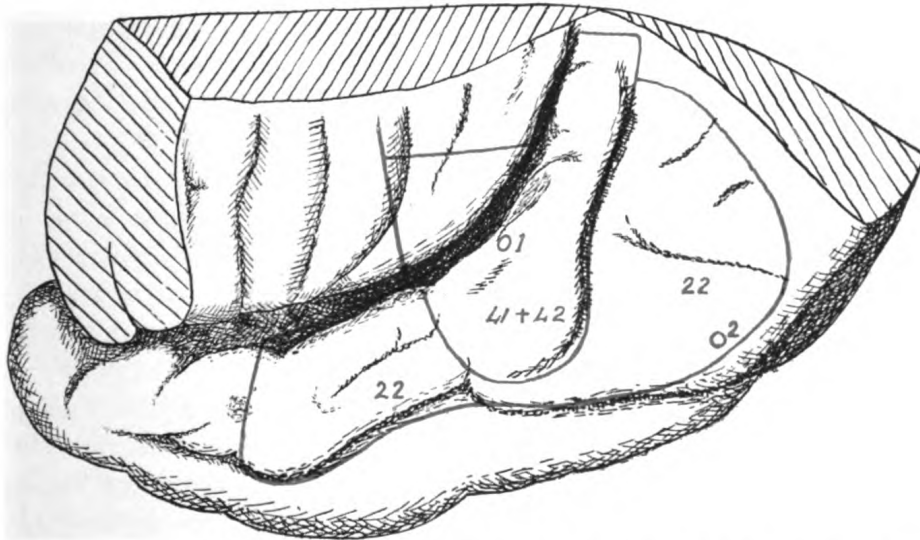


FIG. 2.—Left temporal lobe and insula of a normal woman. Natural size. Signification of the red lines and figures as in Fig. 1.

of the same layer (Figs. 1 and 2). I will not repeat the very correct description of the other characters of this area by Marinesco and Goldstein, as these characters are, moreover, to be seen in Plate II., fig. 1.

The other parts of the temporal lobe which I investigated in the normal case B, possessed the structure of area 22 (Pl. I., fig. 2). Therefore they deviated, as also Campbell remarks from area (41 + 42), by a reduced number of giant cells, but an increased number of large pyramids in the third layer (Pl. II., fig. 2).

The cortex of the left temporal lobe of the deaf-mute man presented marked differences from the above (Pl. I., fig. 1). The area (41 + 42) was divided according to the line AB into an anterior part wholly destitute of giant cells and a posterior part where the number of giant cells was more than four times reduced (Pl. II., figs. 3 and 4). Besides that, the large pyramids of the third layer were much smaller than in the normal case, especially in the anterior part, although there was no sharp limit as with the giant cells. Plate II., fig. 3, taken from the anterior part of the area (41 + 42) in the deaf mute, and fig. 4 taken from the posterior part show the changes of the cortex as compared with the normal type (Pl. II., fig. 1). The other slight differences I saw in this area were probably not abnormal but due to the normal fluctuating variability. I measured the depth of many parts of the cortex, but noticed it to be everywhere so variable that, in my opinion, changes which are not obvious without measurements can only be proved in a statistical way, *i.e.*, by measuring the cortex of several brains of deaf-mutes.

Area 22 could also be divided into an anterior part without a single giant cell (Pl. II, fig. 5), and a posterior part where again a reduction of about four times occurred. The limit between both parts was the same line AB as found in area (41 + 42) (Pl. I., fig. 1). As in normal cases there were in the deaf-mute less giant cells in the posterior part of the area 22 than in that of area (41 + 42). Other changes did not occur, the large supragranular pyramids were not diminished in size (compare Pl. II., fig. 2, with fig. 5).

A small portion of area 22, occupying the most anterior part of the Heschl-gyrus showed, however, still other changes (Pl. II., fig. 6). Here the cortex was considerably diminished in depth, this being only about two-thirds of the normal depth (compare fig. 6 with fig. 2). Most of all the granular layer was altered. The granules were lacking completely in some spots (fig. 6 to the right), although in other places their number was nearly normal. Consequently the granules did not form a continuous

layer. In the third layer were no giant cells and no large pyramidal cells. For this reason the third layer was very thin, and the same may be said about the layers V and VI. So, in general, this portion of the cortex was very poorly developed. The limit between this degenerated region and the other parts of the area 22 was rather sharp, but it passed very gradually indeed into the anterior part of area (41 + 42).

As by the observed changes the characteristic features of the different areas had almost disappeared, I had some doubt about the anterior border of area 22. But I noticed it where it might be expected according to Brodmann's map (Brodmann '09), and I could easily recognise the neighbouring area by the figure and description given of it by Marinesco and Goldstein ('10).

I now come to the question whether the observed changes must be ascribed to deaf-muteness or not. But before doing so it is necessary to consider my investigations of the second "normal" brain A. This belonged to a woman who was neither an imbecile nor deaf, but who was an alcoholic case. I cut portions of the areas (41 + 42), and 22, of both hemispheres of this brain, and found only very few giant cells, certainly no more than in the deaf-mute; moreover, the large supra-granular pyramids were diminished in size. In consequence the cortex resembled very much that of the deaf-mute. I have not tried in this case to decide the extent of these changes, because the brain as a whole was not well preserved. But the preservation certainly could not account for the disappearance of one particular kind of cell.

After I had observed this alcoholic case I was glad to have an opportunity of seeing the structure of a small part of the areas 22, and (41-42) in both hemispheres of another male deaf-mute. This man, named M. S—, died at the age of seventy-two in Claybury Asylum, where he had stayed for only three weeks on account of melancholia. An acute purulent bronchitis, accompanied by œdema of the glottis and fatty degeneration of the heart, caused his death. He was quite deaf since he had scarlet fever when five years old. He could only pronounce a few words, but he was intelligent, and could read and write the "deaf-mute characters." Brain weight, 1500 grammes.

The brain of this man had two Heschl-gyri on both sides. Area (41-42) had lost nearly all the giant cells and most of the large pyramids on the interior Heschl-gyrus (the one which is nearest to the insula). But on the exterior Heschl-gyrus the large pyramids were normal, whereas the number of the giant cells had been reduced, although not to such a

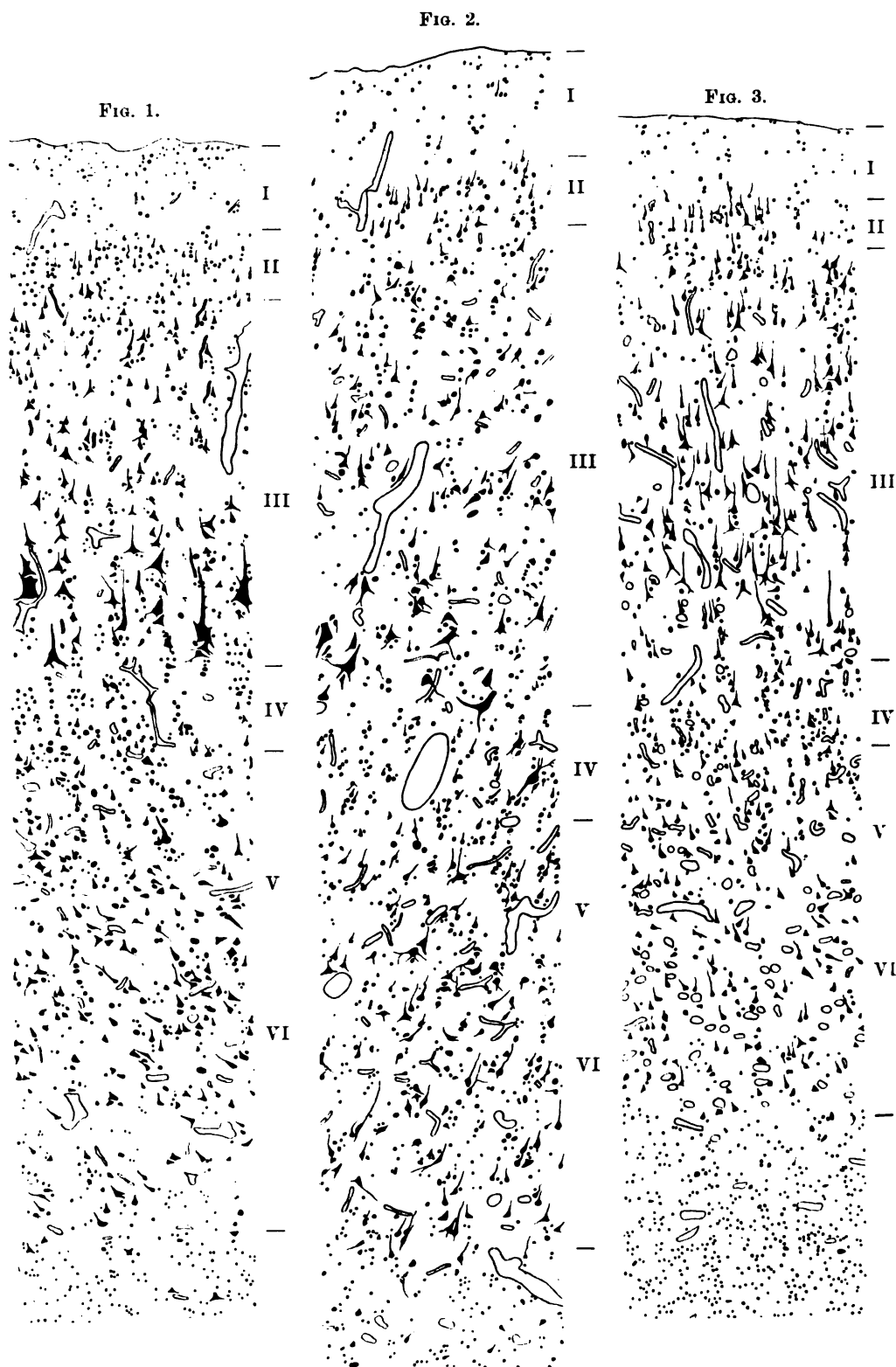


FIG. 1.—Normal cortex of area (41 + 42). Three giant cells.

FIG. 2.—Normal cortex of area 22. Three giant cells and one in layer iv.

FIG. 3.—Deaf mute. Cortex of anterior part of area (41 + 42) without giant cells.

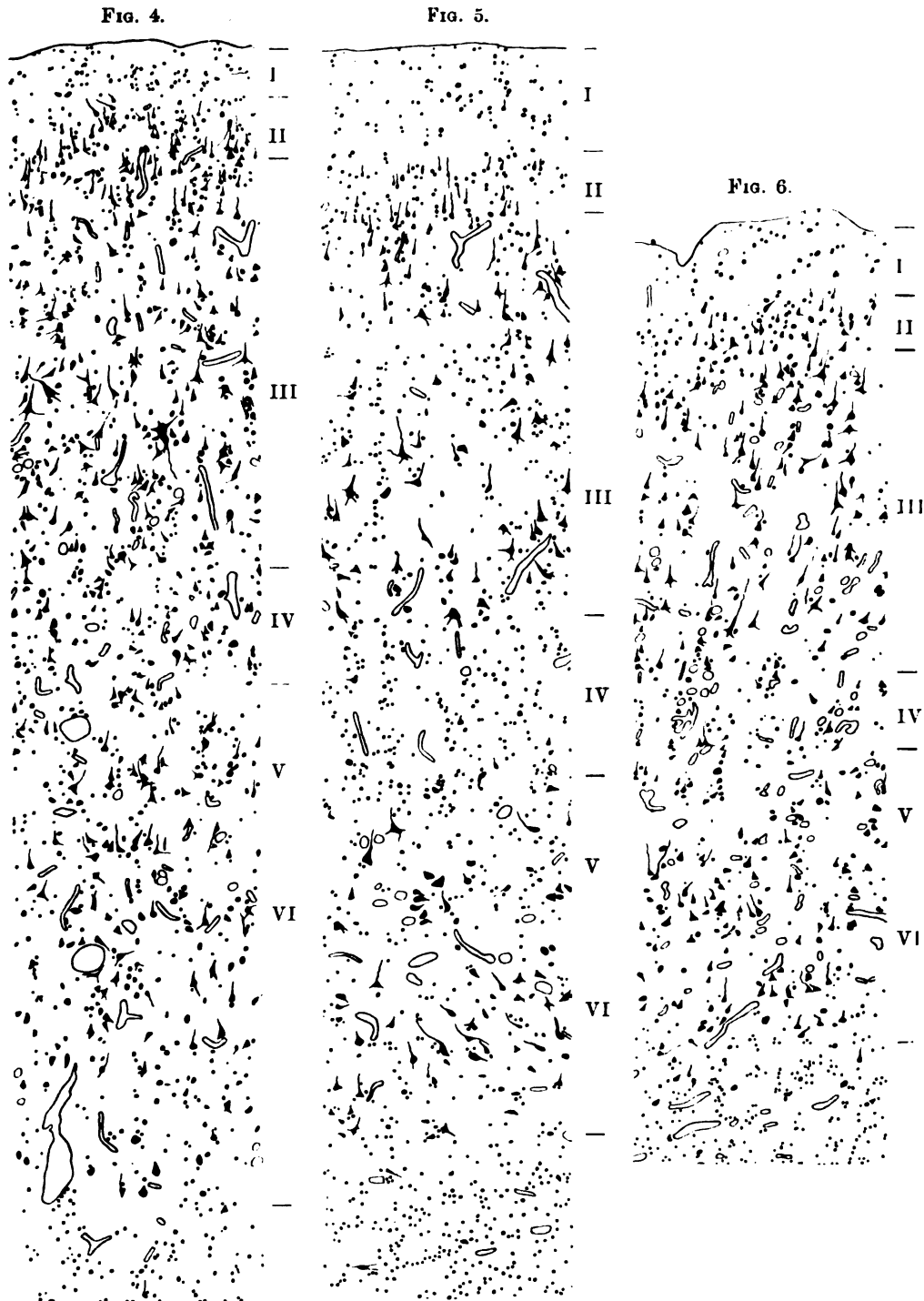


FIG. 4.—Deaf-mute. Cortex of posterior part of area (41 + 42) with few giant cells (one of them in drawing).

FIG. 5.—Deaf-mute. Cortex of anterior part of area 22 without giant cells.

FIG. 6.—Deaf-mute. Cortex of the most degenerated portion of area 22. No granules to the right.

All the sections were cut 10μ in thickness, and all the illustrations are camera lucida drawings (76 Mag.). I, the zonal layer. II, the external layer of granules. III, the layer of supra-granular pyramids. IV, the internal granular layer. V and VI, the layer of infra-granular pyramids and polymorphous layer.

degree as on the interior Heschl-gyrus. These features were noticeable in both sides.

On both sides the studied parts of area 22 showed a reduction of the number of giant cells, and on the left there seemed to be a reduction in the number of the large pyramidal cells.

On the other hand, that the giant cells are normally always present in these regions is proved by the fact that Professor Marinesco was kind enough to inform me, in reply to my question concerning the existence of these cells in normal brains, that he had found "the giant cells in more than forty normal cases, but partly in reduced number in one abnormal case." *

Had I not found the absence of these giant cells in the case of a woman who was not deaf I should, on this evidence, have had no hesitation in associating the deaf-mutism in the cases I have investigated with the disappearance of these cells.

Now I conclude that probably, although not necessarily, there is some causal connection between deaf-mutism and the absence of giant cells. I scarcely dare to connect the changes in the small degenerated region (*vide* fig. 1, pl. I), with deafmutism, although they seem to be more in agreement with the facts observed in previously recorded cases.

I am only familiar with the accounts of two cases of deaf-mutism in which changes have been described as occurring in the auditory cortical centres. The first one is that by Siebenmann and Bing ('07); the second one is the dissertation of Brouwer ('09), where also a review of the literature is given.†

Bing asserts the first temporal gyri, especially the left one, to be narrow in a pathological degree. The cortex of this gyrus is abnormally thin on account of the narrowness of the infra-granular layers and of the layer of the supra-granular "small pyramids" caused by the reduction of the number of their cells. On the other hand, Bing noticed the layer of the large supra-granular pyramids to be undoubtedly broader, although the number of these pyramids was reduced.

Brouwer ('09) describes changes throughout the cortex of the gyri of Heschl, as the internal layer of granules and the polymorphous layer have become narrower, while the infra-granular pyramids have totally vanished.

* Afterwards I myself found in a small part of the Heschl-gyri of another man with normal hearing approximately the same number of giant cells as in my normal brain B.

† Brouwer's results have been published in the German language in 'Die Anatomie der Taubstummheit, herausgegeben von Prof. Dr. Denker, siebente Lieferung; Quix und Brouwer, Beitrag zur Anatomie der kongenitalen Taubstummheit.

My results do not agree with those of Bing or of Brouwer,* but I may remark that the cases of deaf-mutism described by these authors are different in their origin. Bing, as well as Brouwer, have dealt with congenital deaf-mutism, while in my case an inflammation of the ear was the cause of the deaf-muteness.

The assertion of Bing that the number of large supra-granular pyramids in the first temporal gyrus has been reduced is only true in my case so far as it concerns the giant cells, about which Bing does not speak, but which he probably includes in the large pyramids. I could not verify Bing's other statements.

The reduction of the infra-granular pyramids in the Heschl-gyrus is, as also Brouwer ('09) remarks, perhaps not connected with deaf-mutism. Their existence in the normal state has been long a point of controversy between authors; and Marinesco and Goldstein ('10) say that the number of the larger cells in this layer is very variable. Therefore I am not in a position to assert that the diminution in development of the infra-granular pyramids in my case of deaf-muteness was due to pathological conditions. The other changes described by Brouwer were not visible in my case, unless it be in the small degenerated area described above.

In conclusion I cannot prove the association of changes in the Heschl-gyrus or the first temporal gyrus with deaf-mutism. As to the reduction of the number of the giant cells the investigation of more cases is desirable.

THE INSULA AND BROCA'S CONVOLUTION.

Since the relation of Broca's convolution and the island of Reil to articulate speech is now the subject of controversy it appeared to me worth while to look for changes in these regions of the deaf-mute's brain. Hearing is the primary incitation to articulate speech, and before any changes could be expected to occur in the cortex connected with the sense of movements incidental to articulation, changes would probably occur in the cortex where the primary incitation to those movements occurs. It is not surprising, therefore, that I did not find any deviation in structure of Broca's convolution which could not be accounted for by a normal variability.

The normal structure of the cortex in the insula is not completely known. Campbell ('05) describes two different areas, the sulcus centralis

* Nor with the cases quoted by Brouwer, except perhaps, if the changes observed by me really have nothing to do with deaf-muteness the case of Lancla, who found the architectonic structure normal everywhere in the temporal lobe and the insula.

insulae being "an approximate, albeit not an absolute, dividing line between the two areas." One difference between these areas is that the granular layer is well developed in the posterior insula, but is hardly recognisable as a lamina in the anterior insula.

Brodmann ('09) too gives a scheme of the insula in which an agranular anterior area and a granular posterior area may be seen with the sulcus centralis insulae nearly as a common border. This border is more exactly the elongation of the sulcus centralis Rolando, which also divides the regio centralis in a posterior granular and an anterior agranular part. But in the text Brodmann mentions the existence of four areas in the insula, although he gives no particulars about them. In this respect he has enlarged upon his former view (Brodmann '05) when he pointed out three areas, one dorsocaudally, one orally and one ventrally situated. He added the dorsocaudal area to be characterised by a well developed granular layer.

Now, in my opinion, a description of the normal structure of the insula, in order to be exact, should be based upon the average of a number of examinations of brains. I shall be content therefore in describing the most obvious facts relating to the structure of this region in a normal brain and that of the deaf-mute. I may at once say there is no essential difference in structure in the insula of these two brains.

I was able to recognise in the insula three areas (Pl. I., fig. 2). In the first place an anterior one agreeing in extent with the anterior area of Campbell and of Brodmann, and having the sulcus centralis as its approximate hinder border. The term "agranular," attached by Brodmann to this area, is not a very satisfactory term, because in the fourth layer there were many granules (especially well seen in the deaf-mute's brain), but scattered amongst them were numerous pyramids. These deprive that layer of the typical features of a granular layer, although it remains a layer with many granules.*

The two other layers were situated in the posterior insula (Pl. I., fig. 2). The most dorsal one is probably the same as Brodmann's dorsocaudal area. It is recognisable by a very well developed granular layer and by some

* This has also been stated by Marinesco in a paper which appeared after this paper was ready for press. He remarks: "En effet, la distinction de l'insula en une région antérieure agranulaire et une région postérieure granulaire est facile à constater. Cela ne vent pas dire que, dans la région antérieure la couche granuleuse soit complètement absente, car j'en ai trouvé une esquisse . . . de sorte que le passage de la III^{me} à la V^{me} ne se fait pas d'une manière tout à fait insensible." ("Recherches sur la cyto-architecture de l'écorce cérébrale, première partie," 'Revue Générale des Sciences pures et appliquées,' 21^{me} Année, 1910.)

giant cells (fewer than in area 22) among the supra-granular pyramids. In the deaf-mute's brain the number of the giant cells was reduced. There are in the normal case comparatively fewer giant cells, and large supra-granular pyramids in the postero-dorsal area of the insula than in the cortex of the Heschl-gyrus. Therefore and because the infra-granular pyramids are far better developed than in area (41 + 42), it is not a portion of this area overlapping the insula, but a separate area.

The cortex of the ventral portion of the posterior insula is distinguished by its granular layer, as compared with the anterior insula and by the absence of giant cells as well as by the poorer development of the granular layer from the postero-dorsal insula. As to the claustrum, it was in the deaf-mute's brain as well as in the normal one—a layer of spindle-shaped cells separated by a layer of fibres from the cortex of the insula.

I could not find enough reasons to discern an area like area 52 of Brodmann ('09) which he regards as a transitional region from the insula to the temporal lobe.

CONCLUSIONS.

As a summary of my results, I may state the following:

1. In a case of non-congenital deaf-mutism the cortex of the Heschl-gyrus and the first temporal gyrus (areas [41 + 42] and 22) contained in parts very few giant cells, and in parts none at all. A small portion of area 22 showed moreover important reductions in the granular layer, the layer of the supra-granular pyramids and the infra-granular layers.
2. The great diminution of giant cells also found in a second case of deaf-mutism may, perhaps, be due to deaf-mutism, but this is not necessary, because it existed too in a case free from this defect.
3. The cortex of the centre of Broca was normal.
4. The cortex of the insula, where three areas could be distinguished, was normal, except that the number of giant cells in the postero-dorsal area was reduced.

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**A Case of Diffuse Cancer, with special reference to the Changes
in the Brain.**

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AND

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THROUGH the kindness of Dr. Mott we are enabled to report this case, which was admitted under his care to Charing Cross Hospital.

CLINICAL NOTES.

B. U—, aged 40 years, housewife. Admitted November 11th, 1908.

The following history was obtained from the patient's husband, the manager of a chemist's shop.

The patient went to bed on Monday night feeling slightly giddy and unwell, a condition from which she had been suffering for some time. At 9 a.m. next morning her husband left her to all appearances quite normal, to go to work. At 8 p.m. her nephew went to see her, and was let in by her as they have no servants; he found her practically speechless, only able to say yes and no, and weak in her right leg and arm, especially the latter. Her husband was sent for, and she was helped upstairs. A doctor saw her that evening. From the fact that she was already dressed to go out, which she does every day in order to have dinner with her husband at his shop, the husband considers the attack occurred about twelve o'clock. On recounting to patient the story by her husband she agreed with these facts, and intimated by gesture that the attack came on about twelve and lasted about ten minutes, and was preceded by a giddy faint feeling, but no headache. During the attack she passed her water under her.

The husband gave the following past personal history: She had a bad attack of rheumatic fever twenty-three years ago, but a voyage to the Cape restored her health. Even now she complains of vague feelings of

pain in her legs, but the husband thinks they are chiefly imaginary. There has only been this one definite attack of rheumatism. Five months ago she went to a doctor as she had noticed her abdomen getting progressively larger. Three months ago she was told that she was pregnant, and she greatly worried over this. There has been morning sickness for the last three months. The doctor who saw her after the fit at home stated that she was not pregnant, and diagnosed an ovarian cyst. Two years ago patient had diarrhœa and took opium, since then she has had free access, on account of her husband's business, to drugs, and has been in the habit of taking up to six drams of laudanum a day. Patient's mother died of stroke at seventy-five. Her husband states that she has passed very little urine lately, and that walking causes her feet to swell considerably.

Present condition.—Patient lies in bed, looking anxious, with her legs drawn up; she points to the umbilical region when asked if she is in pain. She also complains of headache. Complexion very sallow. Eyes appear very glossy. Difficulty in respiration, almost a stridor; well nourished.

On admission, temperature 100·2° F., vomited four ounces, pulse 116, and respirations 22. During Thursday she drank a little milk and swallowed quite normally, although there was some difficulty in getting her to take any food. She only passed six ounces of urine, there was a little incontinence, but the sum total, allowing for this, could not be ten ounces. During Thursday night she vomited a large amount—twenty-four ounces of darkish fluid—and the temperature dropped to 96·4° F.; this was accompanied by a cold clammy condition of the skin. She has a certain amount of loss of control of the sphincter ani, and there is a tendency to diarrhœa.

Cardio-vascular system.—Pulse 116, low tension, regular. Arteries not thickened. The blood pressure was not estimated as the patient's condition was too grave.

Cardiac impulse not seen. Slight presystolic thrill can be felt. Apex beat slightly displaced outwards, but in the fifth interspace. Presystolic murmur can be heard with accentuation of the first sound; all other sounds normal, but barely audible.

Respiratory system.—Respirations 22. A rough examination showed no abnormal phenomena.

Genito-urinary system.—No children according to her statement, but Dr. Eden considered this doubtful. No miscarriages. Amenorrhœa for the past three months. On examination there appears to be a torn

perineum, which patient dates back to childhood when she fell on a spike.

Condition of breasts.—Nipples are not those of a multipara, and the condition of the breasts leads one to negative pregnancy. Incontinence of fæces and bladder present. Urine, sp. gr. 1030, acid, no albumen or or sugar, trace of pus.

Abdomen.—On inspection very protuberant and looks tense. Two or three patches of pigment present over the lower part. The abdominal wall moves but little with respiration.

Palpation.—Very tense, no thrill, too tense to make out anything definite, but there seems to be a tumour rising out of the pelvis. On percussion, resonant above umbilicus, dull below umbilicus to pubes. Auscultation: No foetal heart sounds, no uterine souffle. Dr. Routh inspected her abdomen, and said that the torn perinæum would account for incontinence of fæces. He considered the case not gynæcological.

Nervous system.—She is a right-handed person. Can say “yes” and “no” on questioning. She seems to understand quite intelligently, and instantly demurred when on reading to her the husband’s account erroneous facts were deliberately introduced. Mind quite clear to all appearances. On two or three occasions she has managed to say “will you kindly,” and has said her name. A handkerchief was held in front of patient, and she was asked to shake hands as many times as there were syllables in the name of the object presented to her—this she could not do. There is no alexia; she cannot write properly voluntarily. Patient was too ill to test her power of copying and writing from dictation. There seems to be no apraxia and no astereognosis. On whistling “God Save the King” and suggesting various tunes she picked the right one out.

Cranial nerves.—First to sixth, normal; seventh, weakness on the right side; eighth to eleventh, normal; twelfth, patient’s tongue, which she pulls out with her fingers, deviates to right side.

The condition of the patient was too desperate to allow of anything but crude tests.

Sensory phenomena.—Common sensibility, tactile and pain senses normal. Weakness on whole of the right side, especially right arm, which she can only occasionally hold up a little. Arm muscle, flaccid.

Reflexes.—Babinski present on right side. On Thursday night the knee jerks were increased on each side, and could only be obtained occasionally on the right side. No ankle clonus.

Condition from day to day:

Friday (two days after admission).—Patient continually vomits “coffee ground” material. Cyanosis and laborous breathing; incontinence of fæces and urine. Abdomen tender on palpation; pulse 120; respiration rate increasing from 22 to 44 at 5 p.m. She was allowed two drams opium; this quietened her, and after the administration of oxygen, she ceased to vomit and slept.

Saturday.—Fair night, no more vomiting and no incontinence; breathing more easy. Can speak a few words; is quiet, intelligent and conscious. Takes her food fairly well; pulse better. Given a little oxygen.

Sunday.—Sick once in the night, slept fairly well; complains of no pain; speaks a little; slight stridor. On auscultation moist sounds all over, especially at bases. Feels comfortable, and takes her food fairly well. At 6 p.m. suddenly became worse; respirations rapid and laboured, gurgling during respiration. High tension, rapid pulse. Ether was administered at 8.30, repeated twice. Venesection brought no relief, and the patient succumbed.

Autopsy.—A large cyst of the left ovary, containing cheesy material, probably malignant, was found. Right ovary normal. Six inches above the anus there is an encircling growth and several secondary growths in the liver. Kidneys; interstitial changes. Heart; thickening of the mitral valve; no stenosis, admitted tips of three fingers; no vegetations. Aortic valves healthy. Lungs; congestion of each base, fluid in both pleuræ. Brain; the external appearances were normal, also the basal vessels. No decortication on stripping. In the middle third of the first right temporal convolution, extending deeply into the white matter, was a dark ill-defined patch about 1 cm. long, the consistence of which was normal. In the middle of the thalamus was a small cavity of a few millimetres’ size with unstained walls. The surface of the right insula, especially towards the anterior part, was softer than normal. There was no apparent hæmorrhage.

HISTOLOGICAL EXAMINATION.

In the rectum a typical medullary cancer was found; the left ovary had degenerated into a cancerous mass, colliquative and caseous changes had taken place. It seemed that the primary tumour originated in the rectum, for some sections show the proliferation and spread of the cells from the mucosa into the sub-mucosa. The cells vary in size; they are generally large protoplasmic and show active pro-

liferation. The nests have not the glandular structure, which the more common adenomatous cancer has; we, therefore, consider it to be a medullary cancer. In the liver there were some small secondary growths of a more glandular character; the cells were smaller, and did not show such active mitotic changes. This less active proliferation and more glandular structure may be but an expression of a diminution in the virulence of the growth. We note this, because often the metastasis shows a more proliferative activity, is more atypical, and shows a more marked anaplasia than the primary growth (Hansemann); but Borst also points out that sometimes a metastatic growth may assume a certain similarity to the epithelium of the primary growth, from which it has been detached. In the lungs no secondary growths were found and no microscopical examination was made. The kidneys show a slight degree of sclerosis, but are otherwise healthy.

Brain.—In all the sections of the cortex examined there were some slight diffuse changes and degeneration of the large pyramidal cells, and in the frontal region on each side there were a few lymphocytes in the adventitial sheaths around the vessels. This may have been due to a zonal disturbance of the circulation, a general cancerous intoxication, or a secondary infection of the patient during the last few days of her illness (probably commencing pneumonia).

There were also less diffuse but more striking changes in the vessels and their immediate surroundings, especially in the left hemisphere. Many capillaries show a proliferation of the elements of their walls; large clear cells can be seen containing big nuclei, often vesicular, irregular and showing some karyokinetic changes. The vessels have a more embryonal character, and it is difficult to distinguish the differences between the elements of the intima and the adventitia. These appearances might be compared with those of the small vessels in syphilitic disease of the brain, to which Nissl and Alzheimer have called attention (endarteritis of the small vessels). Fig. 9., Pl. IV., in Alzheimer's work on general paralysis gives a very good idea of the changes found in some of the vessels in this brain; but in this case proliferation of all the coats of the vessels is not so diffuse as in that of syphilis, and many other features are lacking. We found these embryonal vessels in the insula region, Broca's area, and the first left temporal and frontal regions, the latter less marked (the right side shows little indication of these changes).

Here and there we find in the above-named regions areas of many small vessels bound together and cut through like the "bundles of lumina."

described by Alzheimer in paralysis and other processes of inflammatory character in the brain; this appearance is due to a proliferation of vessels with formation of true "packets of vessels." Around these proliferating vessels cellular infiltrations are absent or very slight; but infiltrations are more marked in the same regions around other vessels (generally of a large calibre), and the infiltrating element consists of lymphocytes, and chiefly some large cells, the nature of which is not easy to determine. These cells have a large round nucleus, which may be duplicated, or may be more irregular in form. The nuclei show a distinct chromatin network, often arranged around the periphery containing a clear centre. The body of the cells stains deeply with thionine and hæmatoxylin; around the nucleus there is often a clear zone, and the general form of the cells is round, and about twelve μ in diameter. These cells are not numerous, and generally form rows along the vessels, and may be sometimes found also in the pial meshes. We may assume that, at any rate, some of these cells are degenerated plasma cells. Dr. Mott suggests that they look like the *morular cells*, which he described in the infiltrations of "sleeping sickness," and which Spielmeyer admits to be degenerated forms of plasma cells. Others of the cells show none of the general features of plasma cells, and we may consider them to be polyblasts in the general sense of the word, that is, migratory elements in close relationship to lymphocytes, expressive of a slight but chronic inflammation of the connective tissue. Some of these cells may arise from the adventitial elements; but the typical features of the clasmatoocytes and clasmatoocyte-like, adventitial cells of Maximow are not to be found here.

At first glance these cells appeared of an epithelial nature, and suggested that we might have to do with a metastasis of the brain, for, as stated above, these large cells surround the adventitial sheath as if they had been carried thither through the blood or lymphatic paths. A closer examination showed no nest-formation, but free, non-epithelial, separate elements.

Certainly a metastasis in the brain would not have been impossible from a cancer of the rectum; Bruns has seen one case; but we ought to find as a rule metastases in the lungs (Bruns), which are missing in our case. In the brain the cancerous elements may infiltrate the adventitial sheaths (Buchholz), or the pachy- and lepto-meninges (Saxer, Fischer-Defoy, Dahmen, Scheel, Leegard, Curtius, Tharbitz, Knierim); generally with strong tendency to hæmorrhages.

We have found no embolus of cancerous cells in any vessel, and may

therefore, from the above reasons, dismiss the idea of the commencement of a secondary formation in the brain. Sections were stained to show the glia; but there seems to be no general increase, and only a slight one around some of the vessels. A recent hæmorrhage in the first left temporal convolution was found, showing in parts red cells degenerating, with deposits of pigment. The hæmorrhage has taken place more into the white matter than the cortex, and consists of many small patches, the vessels of which show the above described changes very distinctly. In the left insula some very small hæmorrhages were seen infiltrating the adventitial spaces. The small cyst was considered to be an old lesion.

We will now endeavour to bring into line the symptomatology and pathology. Apart from the intermittent diarrhœa, the growth in the rectum caused no symptoms, a not uncommon feature (Milward), and the metastasis in the ovary admitted of no certain diagnosis.

A presystolic murmur was heard, but the autopsy revealed no apparent stenosis, although there was some thickening of the mitral valves; the patient was too ill for a thorough examination of the heart. We now dwell upon the condition of the nervous system; the patient, six days before her death, had an apoplectic fit, without any, or very slight loss of consciousness, which left her with a typical right-sided hemiplegia, compromising face and tongue, and with increased knee jerks, and Babinski's sign; besides this, there was motor aphasia; she was verbally mute, and could only say—and then with difficulty—such words as “yes,” “no”; “pretty well”; the “Wortrests” so typical of a motor aphasia. No sensory disturbance was discovered. The symptoms pointed to a lesion in the left hemisphere, with loss of function of the left motor area, of some part of the anterior speech area, and probably part of the anterior part of the insula foot of Broca's convolution; it may be a thrombosis of the first and second branches of the left middle cerebral, or a cancerous embolism in the same branches, or from the mitral valve. The symptoms being purely cortical negative a hæmorrhage. Probably “silent thought” was also lost to some extent, as the patient could not recognise the number of syllables in a word. We may assume that the disturbance causing the hemiplegia took place in or near the cortex, and a hæmorrhage on such a large scale in the cortex (motor area, Broca's region) ought to have given a much more severe fit and complete loss of consciousness. We must look therefore to some other disturbance of the circulation less violent and less sudden; in spite of a careful examination of the branches of the middle cerebral, no embolus was found, but some small branches appeared

blocked, and the microscope has revealed coagulated blood within their lumen.

Was this post-mortem coagulation, or true thrombosis *intra-vitam*? The patient only lived six days, insufficient time for proper organisation to appear; no changes in the vessel walls suggesting the possibility of thrombosis were found.

In a case of diffuse cancer a marantic thrombosis is possible without any striking changes in the walls of the vessels. Had there been complete ischæmia of the nervous tissue normally nourished by the blocked vessels for six days, more advanced degeneration would have been found. Now we find in the brain, chiefly on the left side, some uncommon but interesting changes, a slight chronic inflammation, as evidenced by the infiltrations with mono-nuclear elements, partly plasma cells and a proliferation of small vessels. These changes were certainly prior to the fit, and we have no grounds for admitting the commencement of syphilis or paralysis; apart from no history of infection, many other features are missing. The histological conditions are not very obvious, and only a close examination caused their discovery. We therefore consider the partial similarity to syphilis from a histological point of view merely accidental, and consider that they are due to a general intoxication from the cancer. The marked tendency of cancer to cause a proliferation of the endothelium of the invaded lymphatics and blood vessels is said to be due, not to an infection, but as a reaction to the mechanical and chemical irritation. Such an irritation might conceivably cause a reaction in more distant tissues and non-invaded territories, the stimulating toxic substances being carried there by the circulation. We know that in cancer of many organs there are changes in the blood—pernicious anæmia, simple leucocytosis—and in the nervous system—systemic degeneration, mental disturbances (Meyer, Elzholz, Klippel, and Cheatle). Why could not we find some slight process of vascularity in the brain as in many other intoxications and infections?

The changes are most marked in the left hemisphere, and it is not difficult to admit a toxic cause. It is said that arterio-sclerosis predominates in the left hemisphere owing to it having taken over the more directly executive duties. We can explain the hemiplegia with aphasia by a circulatory disturbance of, perhaps, a thrombosis without complete obliteration of the walls, in a hemisphere already slightly affected possessing abnormal capillaries, and an imperfect lymphatic circulation due to partly infiltrated adventitial sheaths. It may seem

strange that the region which shows the most marked macroscopical and microscopical changes, namely, the first left temporal convolution, has given no symptoms. The aphasia has been motor, not sensory, but we know that the posterior speech area (v. Monakow, Mingazzini, Mott) is much larger than it was until recently assumed, and the small patch in the middle of this convolution can be but of little importance; moreover, the critical state of the woman precluded a more thorough examination, and had we gone more deeply into the matter some disturbance in the comprehension of words might quite possibly have been discovered. The small patch in the right thalamus is very old, and bears no relation to the symptoms. The death of the patient is more than explained by her various affections, and is an example of the difficulty of diagnosis in a somewhat disguised primary cancer, and of correlating the cerebral symptoms with a pathological lesion.

Resumé.—A case of primary cancer in the rectum with secondary diffusion, which was associated with some unusual changes of a slight inflammatory and degenerative character in the brain, which the general intoxication may account for. Six days before death a right hemiplegia with motor aphasia occurred, which may be explained by circulatory disturbances (thrombosis of vessels without a complete obliteration). The case is of importance in showing that changes in the brain which are considered as specific of particular diseases, *e.g.*, syphilis and general paralysis, may occur sometimes, more or less marked, without being connected with them.

Editorial Note.—Oppenheim and Cassirer (*Die Encephalitis*) point out that in cases of non-specific encephalitis there may occasionally be found peri-vascular lymphocytosis and plasma cell infiltration.

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The Oliver-Sharpey Lectures

ON

THE CEREBRO-SPINAL FLUID.

*Delivered before the Royal College of Physicians of London on
April 22nd and 29th, 1910,*

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LECTURE I.

Delivered on April 22nd.

THE PHYSIOLOGY OF THE CEREBRO-SPINAL FLUID.

MR. PRESIDENT,—Allow me to thank you and the Fellows of the College for the great honour you have conferred upon me in asking me to give these lectures, which have been delivered in past years by distinguished English physiologists upon subjects having an important bearing upon medical science.

In the selection of a subject for these lectures I felt how desirable it was to follow in the footsteps of my distinguished predecessors in choosing a subject upon which I had spent research and one which at the same time would be of general interest to our profession. I therefore selected the subject of the cerebro-spinal fluid, the physiology of which is barely mentioned in the text-books of physiology, yet as events have shown during the past ten years the investigation of the cerebro-spinal fluid has proved of the greatest value in the differential diagnosis of diseases of the nervous system. I may mention that in the *Revue Neurologique* for the last ten years there are abstracts of 187 papers. I shall deal with the subject under two headings: (1) the physiology, and (2) the pathology of the cerebro-spinal fluid.

A consideration of the physiology of the cerebro-spinal fluid will naturally lead to an inquiry as to its physical and

chemical properties, its source, its destination, and its functions. Before, however, proceeding to discuss these subjects in detail I must devote a little time to a brief historical introduction.

HISTORICAL REMARKS.

In 1769 Cotugno affirmed the presence in human bodies of a limpid and transparent fluid, like spring-water, that bathed the nervous centres. Contugno also found this fluid in fish and turtles, but his researches failed in the dog, why one does not know. A good but short description was made in 1766 by Haller in his researches upon the physiology of the human body. But Majendie first made a complete study of the nature of the pressure, of the movements, and of the rôle of the cerebro-spinal fluid (1825). He thus describes the existence of the fluid :—

Entre la pie-mère et l'arachnoïde se trouve un liquide que je propose d'appeler cérébro-spinal ; il existe chez l'homme et chez tous mammifères. Il sert à combler le vide qui existerait entre le cerveau et le crâne osseux ; il se régénère avec rapidité, peut circuler à travers les ventricules cérébraux et les espaces sous-arachnoïdiens du cerveau et de la moelle. Au moment de l'expiration le cerveau se gonfle ; le liquide cérébro-spinal passe du crâne dans le canal vertébral. Quand on augmente la pression du liquide, on produit des phénomènes de paralysie et, d'autre part, quand par une ouverture on provoque l'issue de ce liquide, le cerveau et la moelle n'étant plus protégés, il survient une débilité et une faiblesse générale de l'animal.

In 1858 Claude Bernard showed a notable quantity of a substance which reduced Fehling's solution. He affirmed that this reducing substance was glucose.

In 1891 Quincke introduced lumbar puncture as a means of treatment for intracranial pressure ; it was tried in meningitis and general paralysis but with no beneficial therapeutical results. The simple and safe nature of the operation, however, led to a number of investigations relating to the cytology of the fluid in pathological conditions by French scientists—viz., Vidal, Sicard, Ravant, Abadie ; and the successful results obtained in the diagnosis of the various forms of meningitis led to its universal adoption as a valuable means of clinical diagnosis ; moreover, it was found that anæsthesia of the lower extremities could be obtained by injection of cocaine, stovaine, &c., into the spinal subarachnoid space by lumbar puncture ; this added a new and surgical interest to the cerebro-spinal fluid.

The discovery by Castellani of the *Trypanosoma gambiense* in the cerebro-spinal fluid of cases of sleeping sickness led to lumbar puncture and examination of the cerebro-spinal fluid for trypanosomes becoming a recognised mode of diagnosis of sleeping sickness. But perhaps the greatest interest has been aroused by the application to the cerebro-spinal fluid of the Wassermann-Neisser serum reaction for syphilis by Plant and others, with the most satisfactory

results from a diagnostic point of view of general paralysis of the insane and, to a less degree, of tabes dorsalis. With this brief introduction to my subject I will pass on to discuss in detail the physiology of the fluid, and I will commence with

THE PHYSICAL AND CHEMICAL PROPERTIES.

The cerebro-spinal fluid is a fluid *sui generis*, for its physical and chemical properties are different from those of any other fluid in the organism; it approaches in its composition most nearly the sweat and the tears. The normal fluid is clear, like water. The specific gravity is 1.006 to 1.008. The cryoscopic point of the fluid is from -0.51° to -0.56° C.—that is to say, the temperature of congelation is very near that of blood (-0.56° C.). It is, practically speaking, devoid of all corpuscular elements and it contains only traces of protein matter, becoming only very slightly turbid on heating. It is alkaline in reaction, the alkalinity being only one-half that of the blood (Cavazzani). Calculated in percentages of sodium hydrate it varies slightly in different animals, and in man in different pathological conditions, but it will be observed from the subjoined figures that the variation is within very narrow limits. On an average it corresponds to 0.1 per cent. sodium hydrate.

Alkalinity of Cerebro-spinal Fluid.

	Per cent.
Male. Dementia (general paralysis?) ...	0.1076 calculated as NaOH.
" " (general paralysis?) ...	0.1056 " "
" General paralysis ...	0.1104 " "
" " " ...	0.1168 " "
" " " ...	0.1249 " "
" " " ...	0.1132 " "
" Delusional insanity ...	0.1120 " "

(Fluids obtained by lumbar puncture during life, all about noon.)

There is no correspondence between the alkalinity and the rate of flow of the cerebro-spinal fluid; but inasmuch as an acid substance is probably formed as a result of activity of the nervous centres it is possible that after normal sleep the alkalinity may be slightly greater than at the end of a day's work. Although nature generally provides some automatic mechanism whereby any excess of products of metabolism are either removed or neutralised by corresponding activity of secretory processes, in this case an increased cerebro-spinal fluid may be expected to flow if my premisses regarding its mode of origin and functions are correct.

Various analyses show that the principal constituent is sodium chloride, but it also contains traces of carbonates, bicarbonates, phosphates, urea, and dextrose. It is probable that the phosphates, bicarbonates, and carbonates contain

relatively more potassium than the salts of the blood, for Geohegan has shown that the ash of the brain in contradistinction to the ashes of all other tissues contained from 20 to 30 per cent. of potassium against 15 per cent. sodium salts.

I have already mentioned that Claude Bernard proved the existence of sugar in the fluid, but examination of fluid obtained from meningoceles led Halliburton to the conclusion that the reducing substance was not sugar but pyrocatechin. He has, however, abandoned that idea and, in my judgment, it would be well if it were no longer mentioned in text-books, as a very able teacher of physiology expressed surprise when I said that glucose was always present in the cerebro-spinal fluid withdrawn during life; this teacher still thought the reducing substance was pyrocatechin. Since I hope to demonstrate the fact that glucose in the cerebro-spinal fluid is very possibly of great importance in the functions of the central nervous system, I wish to emphasise the fact that Professor Halliburton himself has adopted the view that glucose is the reducing substance and is always present in the cerebro-spinal fluid in normal conditions.

Cavazzani describes the presence of glucose in all cerebro-spinal fluids; he asserts that in human cerebro-spinal fluid a diastatic ferment is present but in smaller quantity than in the lymph. I may mention that we have incubated six specimens of sterile cerebro-spinal fluid for two days without the reducing action being materially affected. Sterile cerebro-spinal fluid has been kept for weeks at the room temperature without the reducing action disappearing. Cavazzani drew off 205 c.c. of cerebro-spinal fluid from a hydrocephalic child; this had a specific gravity of 1.008, and contained 0.98 urea and 0.188 glucose-reducing substance. In another case the specific gravity was 1.006; it contained 0.44 urea and 0.185 reducing substance, with 4.479 chloride of sodium per 1000. Cavazzani was able to confirm in these cases his previous results that the alkalinity of the fluid is greater in the morning than in the evening.

Results of examination of the cerebro-spinal fluid in reference to the quantity of sugar in various conditions.—Mr. Sydney Mann has made for me quantitative analyses of the sugar (by the Fehling gravimetric method) in the cerebro-spinal fluid withdrawn by lumbar puncture during life. The amount of glucose varies from 1.2 to 2.5 per 1000; it will be observed that in dementia præcox the quantity is invariably lower than in any other condition.

Reducing Substance in Cerebro-spinal Fluid.

		Per cent.	
Male.	Old hemiplegia syphilitica	0.212	calculated in terms of glucose.
..	General paralysis	0.186
..	Neurasthenia	0.171
Female.	Dementia præcox	0.147
..	" " " " " " " " " " " "	0.146
..	" " " " " " " " " " " "	0.133
..	" " " " " " " " " " " "	0.127
..	" " " " " " " " " " " "	0.126

(Fluids obtained by lumbar puncture during life.)

That this substance which reduces copper salts is glucose is proved by the facts that it gives with phenylhydrazin the crystals of osazone which melt at from 205° to 206° ; it is dextro-rotatory, and by the yeast fermentation test it yields carbon dioxide. We shall consider later its origin in the fluid and its functions.

The gases of the cerebro-spinal fluid.—As far as I have been able to ascertain there is no account of observations on the gases of the cerebro-spinal fluid. I have been long impressed with the importance of investigating this subject. Dr. John Haldane advised me to use Krogh's micro-tonometer for this purpose; the principle underlying the apparatus, simply stated, is the relative increase or decrease in size of a bubble of air after it has been freely exposed to the fluid, the gas tensions of which in relation to the component gases of the air we desire to ascertain. We found that the bubble after exposure to fluid which had been drawn off during life in such a way that it did not come into contact with the air, did not diminish in size; it showed rather a tendency to increase at atmospheric pressure, demonstrating that gas had escaped from the fluid to the bubble of air, and this gas was found to be carbon dioxide.

Before continuing these tension experiments it was deemed advisable to analyse the gases present in the cerebro-spinal fluid, and, with the assistance of Mr. Mann, I have been able to do this by employing a very convenient form of mercury pump invented by Professor T. G. Brodie and Dr. Winifred Cullis for determining the percentages of gases in salt solutions. The preliminary results that we have obtained are shown in the accompanying table:—

Analysis of Gases of Cerebro-spinal Fluid: Preliminary Results.

1. Gases obtained by boiling *in vacuo*.

	CO ₂ .	O ₂ .	N ₂ .
	Per cent.	Per cent.	Per cent.
1. Dementia præcox ...	8.488 ...	0.356 ...	2.25 by volume.
2. General paralysis... ..	11.067 ...	0.237 ...	1.42 ..
3. " "	11.89 ...	0.157 ...	1.02 ..
4. " "	9.18 ...	0.316 ...	1.97 ..
5. " "	11.19 ...	0.079 ...	0.99 ..

2. Carbon dioxide obtained by boiling *in vacuo* with dilute acid.

	Per cent.
1. Dementia præcox... ..	53.21 by volume.
2. Dementia, general paralysis?	54.90 ..
3. General paralysis	56.38 ..
4. " "	61.13 ..
5. " "	56.19 ..
6. " "	54.41 ..
7. " "	54.8 ..
8. " "	54.41 ..
9. Dementia, general paralysis?	54.73 ..
10. " " " "	58.36 ..

It will be observed that varying small amounts of oxygen and nitrogen are obtained, but the amount of carbon dioxide which can be obtained by boiling the fluid *in vacuo*, on an average, is 10 per cent. by volume; this 10 per cent., I may remark, is obtained by five or six successive operations of boiling *in vacuo*, so that it may be presumed this 10 per cent. by volume of carbon dioxide is in loose dissociable combination. If, however, we take 1 c. c. of the fluid and treat with a weak acid in the same way, we then obtain about 50 per cent. by volume of carbon dioxide. Comparing these results with the gases obtainable from lymph or serum we find that:—

	Cerebro-spinal fluid yield. Per cent.	Lymph and serum yield. Per cent.
By vacuum and heating	10	46 by volume.
By acid and heating <i>in vacuo</i>	50	50 ..
Difference representing CO ₂ in stable combination	40	4 ..

It would therefore appear that the carbon dioxide is in a more stable combination in the cerebro-spinal fluid than in the blood. The oxygen and nitrogen in the fluid in all probability did not come from the atmosphere, for the fluid was drawn off into tubes filled with mercury.

As I observed previously, the investigation of the gas tensions of the cerebro-spinal fluid has been deferred, awaiting the results of the experiments just quoted, and at present I am unable to give any figures.

The object of these researches is to see if the cerebro-spinal fluid can, by virtue of its chemical composition and gas tensions, function as the lymph of the brain. It must, however, always be borne in mind that the fluid which we withdraw by lumbar puncture may be the fluid coming from the perivascular lymphatics of the brain diluted by the secretion of the choroid plexus. This fluid does not, however, correspond to ordinary tissue lymph, even if it were diluted, for the following reasons.

The composition of the fluid is against it being a transudation from the blood or a lymphatic secretion, and the following facts prove this conclusion: (1) It contains 0·02 per cent. of proteins against 7 per cent. in blood plasma; (2) it contains 0·02 per cent. of proteins against 4·5 per cent. in body lymph; (3) there is an absence of lipochrome; (4) there are no leucocytes in the normal fluid; (5) in enteric fever there is absence of agglutinins; (6) it has no hæmolytic action on the blood corpuscles of other animals; (7) it contains no alexins.

Moreover, Cavazzani studied the effect of injection of lymphagogues of Heidenhain—e.g., peptone, extract of eel's blood, glucose, chloride and iodide of sodium—and although in some instances the rate of flow was increased, the amount

of ash was not increased. Capelletti has shown that in dogs ether and pilocarpine increase the rate of outflow, atropine and hyoscyamin diminish it, and amyl nitrite produces no effect.

In general with a few exceptions experimental observations on men and animals have shown that drugs administered by the mouth or subcutaneously do not pass into the cerebro-spinal fluid; this rule also applies for bacterial toxins; neither Blumenthal nor Jacob could find tetanus toxin in the cerebro-spinal fluid when injected subcutaneously into goats. Ransom confirmed this in dogs and rabbits, and only in two of many cases recorded have the results of examination shown the tetanus poison in the cerebro-spinal fluid. It has long been known that in the great majority of cases of jaundice the brain is not stained with bile, nor is the cerebro-spinal fluid coloured by the bile. I only remember seeing it on one or two occasions in a large post-mortem experience. Later on I shall consider the effects of injection of toxic and other substances into the subarachnoid space. The facts I have mentioned all speak against the fluid being either a transudation or lymph secretion, although it is generally admitted that the perivascular lymphatics open into the subarachnoid space. Where does it come from?

SOURCE OF THE CEREBRO-SPINAL FLUID.

Willis in 1664 called attention to the glandular nature of certain reddish granulations (the choroid plexus). The cerebro-spinal fluid is found in all vertebrates, and Pettit and Girard in 1902 published a monograph on the secretory function and morphology of the choroid plexus of the central nervous system, which embraced the systematic study of the plexuses in different animals belonging to different classes of vertebrates. They state that Faivre in 1854 affirmed the intimate relation of the choroid plexus with the cerebro-spinal fluid. The works of Luschka, and the more recent work of Kingsburgh, Findlay, Galeotti, Studnicka, together with the physiological researches of Cavazzani and Capelletti, have progressively tended to support this view of the source of the cerebro-spinal fluid.

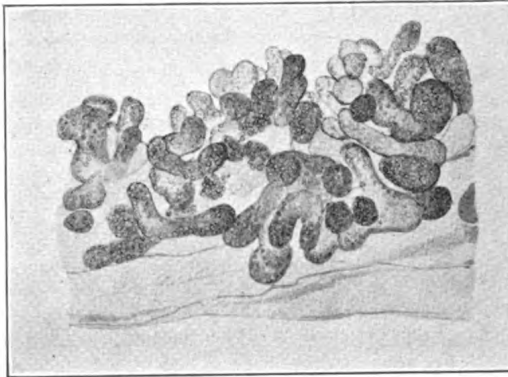
Pettit and Girard have been able to establish a generalised secretory function of the choroid plexus in the different classes of vertebrates; moreover, by the administration of substances endowed with a hyper-secreting action they were able to cause variations in the activity of these structures and corresponding histological changes in the cells covering the plexus.

I have examined the choroid plexus in the human subject obtained in some instances soon enough after death to stain well with the vital methylene blue method. I throw on the screen lantern slides illustrating the structure of the human choroid

obtained from the lateral ventricles. The first is a drawing by Dr. Edgar Schuster of a small piece of the choroid stained by vital methylene blue fixed with molybdate and mounted in Canada balsam; the specimen is not a section but a piece of about the size of the point of a large pin; it is one of the granulations just visible to the naked eye, and this again we see is made up of numbers of microscopic granulations clothed with spheroidal epithelial cells (Fig. 1). The appearance is just such as we would expect if the cells secreted the cerebro-spinal fluid.

In sections under a higher power we are able to make out more definitely the structure of the plexus. Tufts of vessels are seen surrounded by a loose connective tissue covered by a single layer of cubical, spheroidal, or polyhedral cells

FIG. 1.

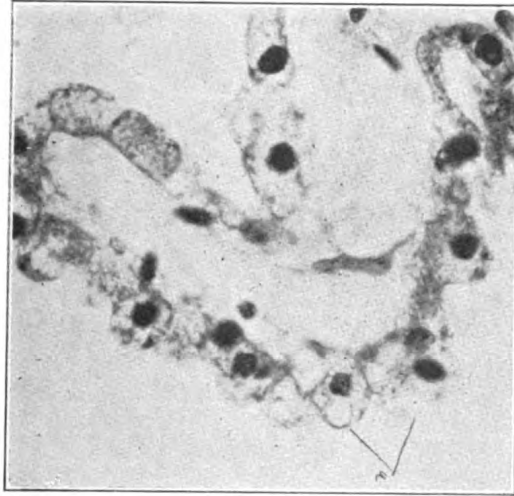


Small choroidal granulation obtained from a sheep's brain immediately after death stained by the vital methylene-blue method of Dogiel. The vacuolated appearance of the cells on their surface is well shown. Magnification 80.

lying on a basement membrane (Figs. 2 and 3). Around the arteries and arterioles and lying in the loose connective tissue numerous nerve fibres are seen in the form of a plexus, but I have not been able to follow the terminal fibrils between the cells. This plexus of nerve fibrils from the choroid plexus of the sheep is well shown in this drawing by Dr. Schuster (Fig. 4).

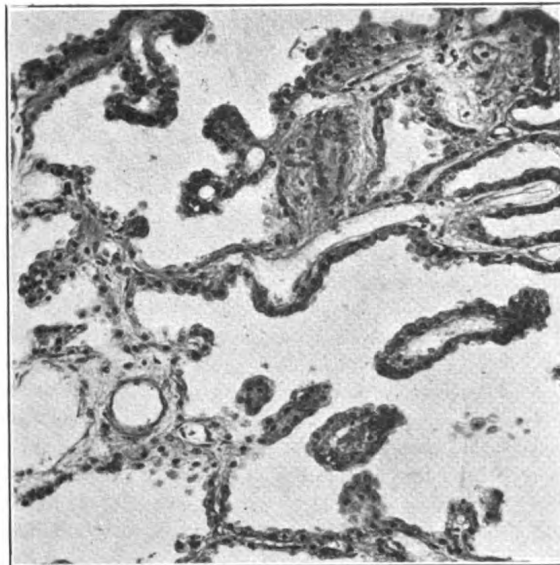
I will now project on the screen a photomicrograph of the human choroid plexus under a magnification of 650 diameters. In one there are many more vacuoles in the cells than in the other. In one cell of this specimen you see a clear vacuole quite near the surface; in the border of the adjoining cell you observe a cup-like cavity, just such as one would expect if fluid had escaped from one of the vacuoles (Fig. 2). Comparison with the lacrymal gland shows

FIG. 2.



Photomicrograph of a section of the choroid plexus of the human subject stained by Giemsa fluid. The cells are all vacuolated: at (a) the section has divided a cell, showing a vacuole, quite superficial; above this there is a cup as if a vacuole in an adjoining cell had discharged the fluid content. Magnification 650.

FIG. 3.

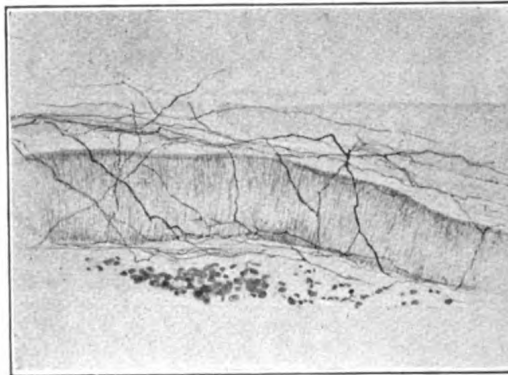


The same section as Fig. 2; the polyhedral cells, supported by a delicate connective stroma, are seen to cover vascular finger-like tufts. Magnification 200.

that the epithelial cells of the choroid plexus present a very similar appearance. The histological evidence is all in favour of the choroid plexus being a gland with an external secretion, but with an internal destination; it would thus constitute a mixed type of gland intermediate between a gland with a duct and a ductless gland. The mode of formation of this gland is effected in an inverse manner, epithelial invagination for the gland with an excretory duct, ependymal invagination for the choroid plexus. In the former case the vascularisation is peripheral, in the latter it is central.

If we can accept these observations as conclusive proof that the choroid plexus is the source of the cerebro-spinal fluid and that it is continually secreting this fluid, then we can understand its unique chemical composition and its freedom

FIG. 4.



A section from the same preparation as Fig. 1 showing a plexus of nerves around an artery; some fibres may be seen entering into the connective tissue stroma of the gland. Magnification 50.

under normal conditions from all corpuscular elements. There is abundant evidence that this fluid is continually being secreted, for Matthieu has collected a number of cases in which large quantities of cerebro-spinal fluid have drained away daily in consequence of injuries of the subarachnoid space by which a communication was established with the exterior. Surgeons have often recorded observations on patients who, after fractures of the base of the skull or extirpation of sub-basilar polypi, have lost large quantities of fluid amounting in the 24 hours, in some cases, to between one and two litres (Billroth, Verneuil, Routier, Tillaux). Halliburton, Hill, and StClair Thomson have also recorded observations of a case of dripping of large quantities of cerebro-spinal fluid from the nose.

An argument in favour of the cerebro-spinal fluid being in

the main secreted by the choroid plexus in the lateral ventricles is afforded by the effects of increased intracranial pressure arising from interference with the escape of the fluid from its principal source in the lateral ventricles. I do not intend to discuss fully the subject of hydrocephalus,¹ but certain interesting cases which have occurred in my practice or have come under my notice at necropsies are instructive. They are cases of internal hydrocephalus caused by non-malignant slow-growing tumours of the third ventricle, and one case of chronic basic meningitis caused by caries of the petrous bone. All four cases had well-marked signs of increased intracranial pressure, vomiting, headache, optic neuritis, tremors, fits, and drowsy stupor, with progressive mental enfeeblement, so that the diagnosis of general paresis was made in all cases except one, which was under my care in Charing Cross Hospital.

The patient was a married man aged 32 years; the first symptom noticed was that while out walking he was attacked with drowsiness and headache followed by a fit; after this he was subject to frequent attacks of a similar nature from which he recovered. Eventually he died, and at the necropsy a small tumour was discovered loosely attached to the choroid, which from time to time could easily have taken up such a position as to block the iter, and thus lead to distension of the third and lateral ventricles of the brain. Seeing that the symptoms came on with drowsiness and headache—this condition ushering in a fit—we may conclude that at this time the tumour had attained such a size that if by chance it fell into such a position as to block up the iter of the third ventricle the fluid secreted by the choroid plexus accumulated in the lateral ventricles, which would, of course, necessitate the prone position and possible dislodgement of the tumour, thereby the escape of the fluid into the subarachnoid space, and sooner or later the return of the patient to his normal state of consciousness, at least this was so in the earlier stages of the illness.

Here we have a condition of cortical anæmia produced followed by the effects like those of an experiment—namely, drowsiness, loss of consciousness, followed by epileptiform convulsions, and towards the end a persistent dulness of comprehension, falling memory, and slowness of ideation, the result of changes in the cortical cells. Doubtless the drowsy stupor and lethargy which come and go in syphilitic basic meningitis are largely due to internal hydrocephalus, produced by the obstruction to the outflow of cerebro-spinal fluid secreted in the lateral ventricles by the choroid plexus. As soon as the pressure rises to a certain degree the obstruc-

¹ The subject is very fully treated by Sir T. Barlow and Dr. Lees in their article, Simple Meningitis in Children, *System of Medicine*, Allbutt, vol. vii.

tion is overcome, and an escape takes place into the subarachnoid space, whence it can flow from the cranial cavity in the manner previously indicated.

These symptoms of internal hydrocephalus, moreover, support the view that the cerebro-spinal fluid is, for the most part, secreted by the choroid plexus contained in the lateral ventricles.

In support of the statement that the choroid plexus secretes the cerebro-spinal fluid, I may mention that at the last meeting of the Physiological Society Halliburton and Dixon stated that an intravenous injection of the saline extract of the choroid plexus produces in dogs a marked increase in the rate of flow of the fluid from the cannula placed in the subcerebellar cisterna. Extract of the brain produces the same result but not so marked.

DESTINATION OF THE FLUID.

The fluid secreted in the ventricles escapes from the fourth ventricle into the subarachnoid space by the foramen of Majendie and the foramina of Luschka.

The foramen of Majendie.—When the cerebellum is raised posteriorly so as to expose the tela choroidea one sees at the level of the point of the calamus scriptorius a round or oval opening with irregular borders as if torn. This orifice connecting the fourth ventricle with the subarachnoid space was first pointed out by Majendie, and has since been called after its discoverer. It is situated in the mid line and measures 7-8 mm. in length by 5-6 mm. in breadth.

Foramina of Luschka.—These are a pair of lateral orifices connecting the fourth ventricle with the subarachnoid space. They occupy the external extremity of the lateral recess which the cavity of the fourth ventricle forms and from which emerge the origin of the mixed nerves. Through the foramina of Luschka the choroid plexus of the fourth ventricle passes.

The existence of the foramen of Majendie has been doubted by Cruveilhier, Reichert, and Kölliker who regarded it as an artifact. The foramina of Luschka have been described by Marc Sée and Hess. The last-named anatomist met with them 51 times out of 54 subjects examined; they are, therefore, nearly constant.

The fluid having escaped into the subarachnoid space fills up all the spaces, cracks, and crevices; at the base of the brain, therefore, it is more abundant than on the convexity; it forms what are termed lakes, rivers, and rivulets (cisterna and flumina). The quantity of fluid contained in the subarachnoid space, ventricles of the brain, and central canal of the spinal cord is about 100 c.c. to 130 c.c., and there is every reason to believe that this fluid is continually being secreted, for experiments on animals and observations on man show that a large quantity of cerebro-spinal fluid can be drawn off by lumbar puncture and soon be replaced. But the fluid cannot be continually secreted and not flow away. According to one view, it escapes along the lymphatics of all

the cranial and spinal nerves, thus reaching the receptaculum chyli and thoracic duct, passing through the paravertebral lymphatic glands in its passage, and eventually, therefore, arriving in the venous circulation.

Flatau's experiments by injection in the rabbit (*viâ* the olfactory nerve in particular) demonstrate that the fluid follows the course of the perineural sheath; then passes directly into the lymphatic networks of the nasal mucosa; thence it arrives at the glands of the neck and the nasopharyngeal cavity; but, according to Flatau, the injection never runs to the surface of the mucosa, as Retzius asserted. Some of the cerebro-spinal fluid probably does escape along these perineural lymphatics, and it is probable that these are the avenues of infection in the production of tuberculous, syphilitic, epidemic, and pneumococcic meningitis.

However, the observations of Leonard Hill and Cushing favour the view that the fluid contained in the cerebral subarachnoid space and perivascular canalicular systems finds its exit from the cranium by means of the veins opening into the longitudinal sinus. Hill found that

Saline injected at any pressure above the cerebral venous pressure disappears from the cranio-vertebral cavity; the higher the pressure, the more rapid its disappearance. As a result of injecting saline coloured with methylene blue, fluid can be traced passing straight into the venous sinuses. In so short a time as 10 to 20 minutes, the blue colour may be found secreted in the stomach and in the bladder. On the other hand, the lymphatics in the neck in so short a time are not coloured. After an hour's steady injection the deep cervical and lymphatic glands are seen to be only partly tinged with the blue colour.

Cushing, after producing intracranial pressure by injection of normal saline solution, states that the fluid does not escape readily from the subarachnoid cavity; even under pressure not more than from 60 c.c. to 100 c.c. escape in half an hour perhaps. He agrees with Adamkiewicz that there exists a free communication between the subarachnoid space and the longitudinal sinus. He questions the correctness of Key and Retzius's hypothesis that the Pacchionian glands act as a filter, for, as he remarks, they do not exist in very young children or in some of the lower animals. The nature of these openings of the subarachnoid space is not known, but probably they run obliquely forwards, like the veins, into the sinus, and have, like them, a valvular action, so that the fluid can flow into the sinus, but blood cannot flow back. Mercury injected into the subarachnoid cavity found its way into the sinuses, jugular veins, and right heart. A non-absorbable gas introduced into the subarachnoid space produced death by cardiac air-embolism, and, if the jugulars were exposed, bubbles of it could be seen pouring down towards the heart. Exposure of the cervical lymphatics and of the thoracic duct, on the other hand, showed in all instances a complete freedom from gas.

Reiner and Schnitzler injected a saline solution of potassium ferrocyanide into the cranium. This salt very rapidly appeared in the jugular vein. The venous flow was quickened by the injection. On the other hand, injection of olive oil caused compression of the cerebral vessels, and slowed the venous outflow. This rather supposes another way of escape, and I venture to suggest the cerebro-spinal fluid may get into the venous blood by the capillaries.

Before giving my reasons for this hypothesis it will be necessary to give a description of the lymphatic sheaths of the vessels of the brain. Testut thus describes the perivascular lymphatics. Robin in 1858 proved the existence of a membrane surrounding the vessels of the central nervous system in the form of a sleeve, leaving an interval between it and the vessels; it is a membranous tube in which the blood-vessel is, as it were, suspended. This is the lymphatic sheath.

The wall of this sheath is very delicate and is continuous with the tunica adventitia. It is constituted, at least for the larger vessels, of extremely fine and delicate bundles of connective tissue which are the branches of flattened plate-like cells of a fusiform or polyhedral shape. The external surface of the sheath is formed by the nervous substance. Its internal surface is towards the vessel from which it is separated by a space which surrounds immediately the vessel. This space which separates the vessel from the pial sheath is traversed by very fine trabeculae which extend from its external to its internal wall. It is filled by a *clear and transparent fluid* which from the point of view of its morphological significance should be considered as lymph. It contains in variable amount lymph corpuscles, fatty granules, and sometimes even drops of oil. The lymphatic sheaths are observed in the venules and the arterioles, but they are always better developed on the latter than on the former. At the place where the arteriole divides into capillaries, the lymph space terminates in a cul-de-sac; it is not only that the sheath ceases to exist but at this situation it is applied against the wall of the capillary, leaving no recognisable space between them.

The lymphatic sheaths open into the subarachnoid space, which thus become their common rendezvous; *vice versa* it may be asserted that the lymphatic sheaths of the vessels of the central nervous system are intracerebral and intraspinal prolongations of the subarachnoid space. Eberth has pointed out the existence of a continuous endothelial covering on one or other of the walls. This endothelial covering also occurs on the trabeculae which traverse the lymphatic space. His by successful injection experiments has proved the existence of two sheaths, the adventitial sheath of Robin, and another periadventitial which surrounds it like a sleeve. His affirms that the two sheaths are entirely independent of one another;

that is to say, there is no intercommunication. On the central side the periadventitial sheaths are connected with the pericellular spaces. On the peripheral side they end in a series of lacunæ which occur between the external surface of the central nervous system and the pia mater which covers them; according to the region these are termed epispinal, epicerebral, and epicerebellar spaces of His. Testut remarks that the periadventitial sheaths are considered by some anatomists to be artifacts and have not the same significance as the pericellular spaces. They are simply interstices nearly virtual in ordinary conditions, but, in consequence of injection or of pathological conditions, capable of enlarging and acquiring a real capacity. As in the adventitial sheaths, the lymph circulates from within out and very probably passes by simple filtration into the subarachnoid space by at present little understood communications.

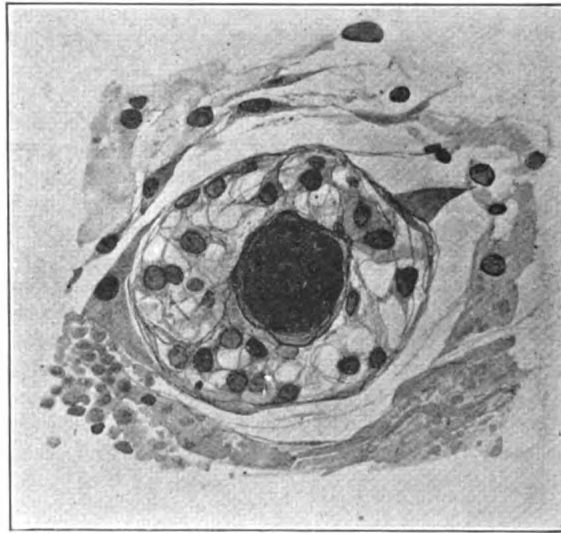
A study of the histological conditions met with in the perivascular sheaths in chronic meningo-encephalitis of syphilis, general paralysis, and sleeping sickness throws some light upon the structure of the perivascular lymphatics; in the normal state the structures are too delicate to permit of clear observation, but when owing to chronic irritation the morphological elements actively proliferate, it may then be seen that the appearances coincide with those of chronic inflammation of lymphatic structures elsewhere in the body. Sleeping sickness offers the best material for the study of the perivascular sheath; in this disease the connective tissue cells of the pial sheath proliferate and form a dense network, in the meshes of which are abundant lymphocytes and plasma cells. I came to the conclusion that the plasma cells and the lymphocytes were the result of the proliferation of the endothelial cells. This chronic perivascular lymphatic cell proliferation is the same as, and continuous with, the cell proliferation of the lepto-meninges. It is associated with a proliferation of the special connective tissue elements of the nervous system—the neuroglia (Fig. 5). The normal cerebro-spinal fluid contains no cell elements, but in all affections causing a chronic meningo-encephalitis the fluid contains lymphocytes, generally speaking, in proportion to the severity and widespread extension of the meningo-encephalitis, whether it be due to syphilis, parasymphilis, sleeping sickness, or tuberculosis.

I have studied the histology of the perivascular lymphatics in the brains of animals in which Dr. Leonard Hill had produced experimental anæmia by ligation of three or more of the cerebral arteries—e.g., two carotids and one vertebral in monkeys, the animals dying or being killed at various periods of time after the operation. The vessels, especially the arteries, arterioles, and capillaries, are in consequence of the ligation of the trunk arteries empty and collapsed, yet the brains on exposure were not shrunken; they were quite

pale and watery, and microscopic examination indicated that the reason that the brains had not shrunk was the fact that the cerebro-spinal fluid had filled up the spaces which would otherwise have existed from the blood-supply having been cut off. Small portions of the brains were generally hardened in alcohol, but specimens were prepared from one monkey's brain in which experiment two carotids and one vertebral were ligatured, the animal dying 23 hours after. The brain of this monkey was removed and placed in Mann's picric and perchloride of mercury solution (Figs. 6 and 7).

Most of the experimental anæmic brains of the monkeys

FIG. 5.



Inflamed lymphatic sheath of a small spinal artery in a case of punctate syphilitic myelitis. The proliferation of the branched connective tissue cells of the pial sheath is well seen. Drawing by Dr. Edgar Schuster. Magnification 650.

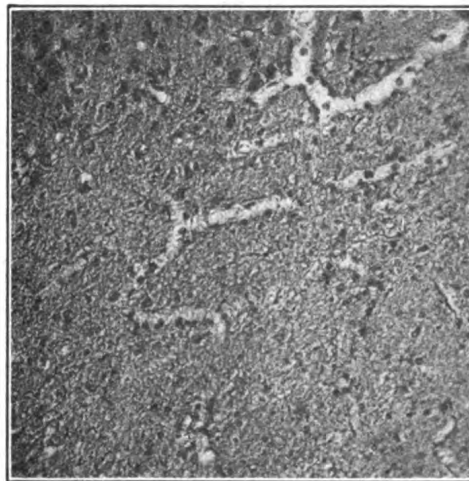
that died as a result of the ligature of the vessels showed a perivascular canalicular system continuous on the one hand with the perineuronal spaces, and, on the other hand, with the subarachnoid space. The perivascular spaces are clear and transparent, therefore they cannot contain ordinary lymph because an amorphous deposit of coagulated albumin would have been precipitated by the perchloride and picric fluid. It cannot, however, be an empty space, and seeing that it is continuous with the subarachnoid space it is reasonable to presume that it is filled with cerebro-spinal fluid. It is not an artifact due to the hardening, otherwise the delicate strands of connective tissue which you

FIG. 6.



Photomicrograph of the brain of a monkey—experimental anæmia—showing two vessels with the dilated perivascular lymph sheaths continuous with the subarachnoid space; both are distended with a clear fluid; fine trabeculae can be seen stretching across from the wall of the vessel to the nervous substance, therefore the dilatation is not due to an artefact. Magnification 200.

FIG. 7



Photomicrograph of the subcortical white matter of the same specimen as Fig. 5, showing the dilated perivascular lymph spaces distended with a clear fluid; the contained blood-vessels are collapsed and empty. Magnification 200.

see stretching across the space would not be present. In another section of the same brain this canalicular system is shown surrounding the smaller vessels and connected with the perineuronal spaces, and here again it may be observed that there is no evidence of any protein-containing lymph (Fig. 8). Occasionally the perineuronal spaces can be seen in direct communication with the space around a capillary (Fig. 9). These perineuronal and perivascular lymphatic spaces and their interconnexions can only be seen in abnormal conditions. In experimental anæmia a space can

FIG. 8.



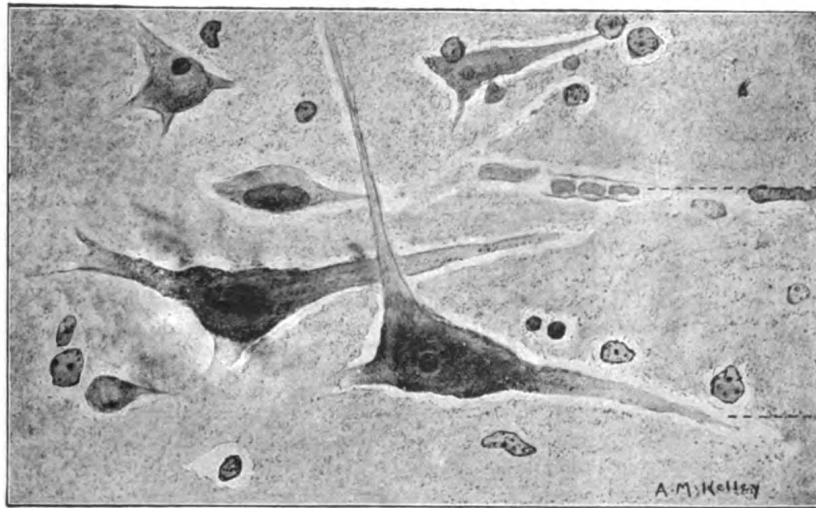
Photomicrograph of the cortex cerebri of a monkey. Experimental anæmia. The dilated perivascular spaces are seen to be connected with the dilated perineuronic spaces; this is rendered clear by the empty condition of the small blood-vessels. Magnification 250.

be seen around the capillaries, and stretching across from the wall to the surrounding nervous tissue are delicate connective tissue threads, as this photomicrograph shows. It would thus seem probable that a canalicular system surrounding the cells and vessels of the brain exists which is in direct communication with the subarachnoid space. This canalicular system contains a fluid of non-protein nature (probably, therefore, the cerebro-spinal fluid), which may serve as the ambient fluid of the neurons and play the part of lymph to the central nervous system.

I will here quote a passage from the article on Meningitis

by Sir T. Barlow and Dr. Lees. "We may here add that cerebro-spinal fluid as obtained from any point below the fourth ventricle cannot be an absolutely pure secretion; it must contain waste products resulting from cerebral metabolism, ~~for~~ into the subarachnoid space surrounding the brain open the lymphatic sheaths of all the cerebral arteries, and Dr. Bevan Lewis has shown that the nerve cells of the brain are placed within pericellular sacs, each of which has a definite lymphatic connexion with the wall of a small blood-vessel."

FIG. 9.



Drawing of a small portion of Fig. 1. The large pyramidal cells are seen with their perineuronic spaces filled with a non-coagulated fluid. The apical process of one cell is seen in a canalicula which is directly connected with a space around a capillary. Magnification 500.

MECHANICAL EFFECTS OF THE CEREBRO-SPINAL FLUID.

The blood-vessels of the cerebro-spinal axis have comparatively thin walls, and the arteries relatively few muscular fibres and vaso-motor nerves. The uniform pressure of the fluid sleeve which surrounds the blood-vessels serves to support their column of blood. The whole central nervous system being contained in a closed space, the cerebro-spinal fluid fills up all the space which is not occupied by tissues or blood, serving thereby to equalise the pressure throughout the whole cranio-spinal cavity; moreover, it acts as a water cushion, especially at the base of the brain, protecting the vital structures of the medulla from the shock of commotion and concussion. It serves also as a

self-adjusting mechanism by maintaining a uniform equalisation of the blood-supply to the nerve elements during the rhythmical variations of respiration and circulation. The question arises, does it play the part of the lymph?

FUNCTION OF THE CEREBRO-SPINAL FLUID.

If the cerebro-spinal fluid serves as the lymph of the brain, it may be asked, How is it that generally, with few exceptions, experimental observations on men and animals have shown that drugs and bacterial toxins administered by the mouth and subcutaneously do not pass into the cerebro-spinal fluid? Experiments, however, have shown that very much smaller quantities of these same drugs and bacterial toxins injected into the cerebro-spinal fluid of the sub-arachnoid space produced much more marked and a much more rapid onset of symptoms.

Thus Lewandowsky observed that a few centigrammes of sodium ferrocyanide injected into the subarachnoid space rapidly produced toxic symptoms, whereas from 4 to 6 grammes injected into the jugular vein in rabbits of the same weight produced no specific symptoms. This was not due to the salt solution employed, for a 10 per cent. saline solution injected into the subarachnoid space produced only slight effects.

Behring found that hens injected subcutaneously or intravenously with tetanus toxin suffered no effects, whereas when it was injected into the cerebro-spinal fluid they died from typical tetanus.

Jacob after introduction of methylene blue and iodine into the cerebro-spinal fluid was able to demonstrate their presence in the brain several days later, although these substances were now no longer present in the cerebro-spinal fluid. These researches indicate that substances in the cerebro-spinal fluid can directly act upon the ganglion cells of the brain and spinal cord. Lewandowsky affirms that this takes place by way of the lymph channels.

According to the anatomical proofs of Schwalbe, Key, and Retzius and the physiological observations and experiments of Quincke and Jacob, the perivascular lymphatics open freely into the subarachnoid space. They injected methylene blue and cinnabar, also ferrocyanide of sodium, converting the latter into Prussian blue, and showed in a most convincing manner under the microscope the existence of the substances injected in the perivascular spaces. Lewandowsky, after injection of methylene blue, also observed imbibition phenomena which were likewise observed by Bruno.

This experimental evidence tends to support my contention that the cerebro-spinal fluid comes into relation with the nerve-cell elements and therefore may be the ambient fluid. But if substances are unable to pass from the capillaries into

the lymph spaces, experiments show that substances are able to find their way rapidly into the blood when injected into the subarachnoid space. This may be by the channels already alluded to. But I have shown that the perivascular lymphatics open into the subarachnoid space, and if these perivascular lymphatics contained ordinary tissue lymph the cerebro-spinal fluid would contain a very much larger amount of protein and lymph cells than it does; there must be some medium of exchange between the blood in the capillaries and the neurons, and, therefore, why not the cerebro-spinal fluid?

Suppose, then, it be granted that the cerebro-spinal fluid may function as the lymph of the brain, and is the ambient fluid in which exchanges take place between the blood in the capillaries and the neurons, can we explain why substances do not pass out of the capillaries into the fluid? Most authorities are agreed that there is no lymphatic sheath on the capillaries, so that we have only, so far as we know, the wall of the capillary intervening between the blood and a fluid which is similar to blood plasma in its crystalloid diffusible substances although not identical, for its alkalinity is only half that of the blood and the sugar it contains is less.

The force which determines a movement or exchange between solutions in immediate contact separated by a more or less permeable membrane is termed the osmotic pressure. By this force substances dissolved are displaced to situations where they are less concentrated. Water moves in an opposite direction. This movement constitutes the phenomena of diffusion and the osmotic pressure is the motive force which animates matter and produces diffusion of two liquids unequally rich in dissolved molecules separated by a membrane; the more concentrated liquid attracts a portion of the water contained in the less concentrated liquid. The osmotic pressure of a fluid is proportional to its dissolved molecules—in other words, to its molecular concentration. In human physiology the blood serum is generally taken as a standard of osmotic pressure, and the terms isotonic, hypertonic, and hypotonic solutions are terms used in reference to normal blood serum.

Is it a reasonable hypothesis that the osmotic pressure as regards water and carbon dioxide is from the ambient cerebro-spinal fluid to the blood, and that certain of the salts and sugar pass from the blood to the fluid through the wall of the capillary? As we have no precise knowledge of the composition of the cerebro-spinal fluid as it leaves the cells of the choroid plexus, we can only say it is possible that this fluid is not exactly the same in composition as that which is contained in the subarachnoid space. By this I mean to infer that the fluid which is secreted by the epithelial cells of the choroidal gland in its passage from the subarachnoid space along the peri-

vascular lymphatics back to the subarachnoid space may receive substances—e.g., an addition of sugar and possibly some salts. Whether this fluid, as it is secreted by the choroid plexus, is the same as that withdrawn from the subarachnoid space by lumbar puncture is the crucial point which requires to be settled before the hypothesis I would draw can be maintained. The hypothesis is that the fluid as it circulates in the perivascular and pericellular channels may give up water and carbon dioxide and take up oxygen and sugar. Seeing that there is no proof to my mind that the fluid contains a glycolytic ferment, it may, if this hypothesis is true, be assumed that the ganglion cells produce the necessary glycolytic ferment by which the sugar can be converted into neural energy. The observations and experiments are, however, all in a preliminary stage and much work still is necessary before any safe conclusions can be drawn. The results so far obtained, however, are sufficiently encouraging to lead to a continuance of the work. In my next lecture I propose to deal with the subject of the cerebro-spinal fluid from the pathological point of view.

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LECTURE II.

*Delivered on April 29th.*THE PATHOLOGY OF THE CEREBRO-SPINAL
FLUID.

MR. PRESIDENT AND FELLOWS OF THE COLLEGE,—In my last lecture I endeavoured to point out to you the physiology of the cerebro-spinal fluid. I discussed its physical and chemical properties, its source, its destination, and its functions. To-day I propose to consider the pathology of the cerebro-spinal fluid.

I will throw on the screen a lantern slide indicating the pathological conditions which may occur in the fluid.

TABLE I.—*Cerebro-spinal Fluid and Pathological Conditions.*

Properties, substances, &c.	Normal.	Pathological.
Appearance.	Clear, like water.	Serous, turbid, purulent, fibrinous, yellow, red, brown.
Specific gravity.	1·004–1·007.	Increased.
Reaction.	Alkaline.	Alkaline.
Tension.	60 drops per minute.	Hypertension, Hypotension.
Osmoscopy.	–0·56°.	Hyper- Hypo-
Permeability of subarachnoid space.	<i>Nil.</i>	Variable and unstable.
Presence of drugs.	—	Occasional instances.
Toxicity.	<i>Nil.</i>	It does exist, but rare.
Virulence.	<i>Nil.</i>	Sometimes marked.
<i>Chemical Alterations.</i>		
Proteins.	Trace globulin. No albumin.	Excess globulin, albumin, nucleo-protein.
Lipoids.	<i>Nil.</i>	Cholesterol. Splitting products of lecithins and sphingomyelin.
Sugar.	0·15–0·18%.	Excess in diabetes. Probable decrease in dementia præcox.
Urea.	0·15%.	Excess in uræmia.
Choline.	<i>Nil.</i>	Probable trace in acute nervous degeneration.
Chlorides.	0·6–0·7%.	—
Carbonates.	0·13%.	—
Potassium salts.	0·03% KCl.	No appreciable alteration.

PROPERTIES, SUBSTANCES, &C.

First as regards its physical properties. Even in marked pathological conditions, such as general paralysis of the insane, the fluid may appear clear like water, and only on further investigation may its pathological changes be discovered. Occasionally, however, the fluid may be turbid, purulent, serous, fibrinous; its colour may be yellow, being tinged with bile, red from the presence of blood, or brownish-red from the presence of altered blood. In my experience, however, which is a large one, I have very seldom seen the fluid other than like clear water, excepting always the presence of blood from the puncture of a small vessel during the performance of the operation. There is little to be said about its specific gravity, nor about the reaction. A rough estimate has been made of the tension by the number of drops per minute; 60 drops is considered the normal average. With hypertension an increased number of drops will occur.

As regards the rest of the table there is little to be said except as to the presence of drugs. As a rule drugs do not pass into the cerebro-spinal fluid, and most observers have not confirmed Majendie's original observations relating to the passage of potassium iodide into the cerebro-spinal fluid, a fact upon which Majendie laid great stress as showing the manner in which this drug benefited in such a marked degree certain diseases of the nervous system. Recently an important observation has been made by Ager. He has obtained satisfactory results following the administration of urotropine in meningeal affections; the drug is said to be excreted in the cerebro-spinal fluid in half hour to one hour after ingestion, and to exert a marked antibacterial effect. It was first employed in a case of cerebro-spinal fistula following trephining for cerebral tumour, in which the discharge became purulent. After the administration of 30 grains daily for a week the temperature became normal and recovery ensued. Experiments made on animals have been confirmatory. It is known that tetanus toxin does not pass into the cerebro-spinal fluid, but to this I have already referred in my first lecture. I may, however, remark that we should not expect the tetanus toxin to be eliminated by the choroidal gland, but from the capillaries in the nervous substance. Here the affinity of the toxin for the nervous matter would exert itself immediately. Upon the escape of the toxin from the blood-stream there should be in consequence no toxin free to pass into the sub-arachnoid space from which the fluid is withdrawn.

CHEMICAL ALTERATIONS.

I will now pass on to certain chemical alterations, dwelling more especially upon those to which we have given attention in the laboratory at Claybury.

Proteins.—The amount of protein in normal cerebro-spinal fluid is especially low (about 0·03 per cent.); serum-globulin may be present in slight amount, but albumin is absent. In acute and chronic inflammatory conditions, in fact in all conditions where there is leucocytosis, there is excess of globulin, and albumin and nucleo-proteins are present. In cases of progressive degeneration, in spite of the large excess of fluid, the amount of proteins is found to be greatly increased. This excess consists of globulins, nucleo-proteins, and a small amount of albumin, the greater part being coagulable by heat between 73°–80° C. The excess of globulin is the most marked, and Noguchi describes the following method for its detection in a small quantity of *blood-free* cerebro-spinal fluid. Boil for a few seconds two parts of the cerebro-spinal fluid with five parts of a 10 per cent. butyric acid solution (in 0·9 per cent. sodium chloride solution); then add one part of normal sodium hydrate solution (4 per cent.) and boil again briefly. Noguchi states that the fluid of parasyphilitic cases gives a granular or flocculent precipitate on allowing the tube to stand for a short time, and that cases of alcoholic psychosis, dementia præcox, imbecility, epilepsy, and many other non-specific diseases do not give any precipitate, but that cases of tuberculous meningitis, pneumococcic meningitis, and epidemic cerebro-spinal meningitis give an enormous amount of precipitate. I have applied this test to a considerable number of fluids, and have obtained a positive reaction in many non-specific cases, in fact, in all cases of dementia, whether non-specific or specific, and have found that the amount of precipitate is proportional to the degree of degeneration of nervous tissue, being most marked in the progressive degeneration of general paralysis of the insane. Another test for the globulin present consists in allowing the fluid to flow gently on to the surface of a saturated solution of ammonium sulphate, when a characteristic white ring appears which intensifies on standing. A rough indication of the excess of protein can also be obtained by precipitating the total protein content of the cerebro-spinal fluid with three times its volume of absolute alcohol after rendering it faintly acid with acetic acid.

Lipoids —In the normal fluids no lipoids are present, but in degenerative conditions of the nervous system, whether primary or secondary, lipoids are present in the form of cholesterol, or, as it was formerly termed, cholesterin, an

alcohol of the terpene series containing neither phosphorus nor nitrogen. This substance, the method for detecting which I shall point out presently, we have found present in practically all cases of general paralysis and chronic dementia. Generally speaking, the amount present, as shown by the intensity of the colour reaction, is proportional to the amount of wasting. It is of interest to note that frequently in cases of chronic dementia and chronic wasting diseases of the brain and spinal cord cholesteatomata of the meninges are found, and I have even seen little plates and nodules of a cholesterin-containing substance. The term cholesteatoma was given to those bodies owing to the fact that crystals of cholesterol are often found in their centre. Besides cholesterol there are phosphatides, the result of cleavage products of the lecithins and sphingomyelin.

The presence of lipoids is of interest and importance because they are indicative of wasting of the nervous structure. Moreover, they are of importance in connexion with the Wassermann reaction. Pighini asserts that cholesterol is essential for the Wassermann reaction, but inasmuch as we have found it in the fluid of diseases which do not give the Wassermann reaction, I do not agree with this statement. It seems much more likely that the Wassermann reaction—a subject to which I shall allude much more fully later—is connected with a particular form of eu-globulin.

Sugar.—The quantity of sugar varies in amount. Probably the normal quantity in fluid withdrawn by lumbar puncture is 0.15 to 0.18 per cent. If we could obtain it from the subarachnoid space without admixture of the fluid as it is secreted by the choroid plexus, it would possibly show a higher percentage, approximating that of the blood. It has long been known that the sugar is increased in diabetes, and that it diminishes under the influence of treatment. The relatively small percentage of sugar in the cerebro-spinal fluid of cases of dementia præcox is interesting, and if in a large number of cases we find this diminished quantity prevails, the fact might be correlated with the clinical symptoms of this disease.

Urea.—I have not made any estimations of urea. The normal quantity is 0.15 per cent., and numerous observers have shown that there is an excess in uræmia.

Choline.—Professor W. D. Halliburton and I made a number of observations tending to show that choline occurs in the blood and cerebro-spinal fluid in conditions where a large amount of nervous tissue was undergoing degeneration. The existence of choline was demonstrated by physiological and micro-chemical tests. I am, however, of opinion from further observations that the micro-chemical tests employed—i.e., the formation of choline

platino-chloride crystals—were unreliable, and that the crystals we obtained were more often potassium and ammonium salts; moreover, a number of post-mortem fluids were used for our observations, and in the laboratory we have found, using the periodide test (investigated by Rosenheim), that a very small quantity of fluid obtained from any post-mortem within a comparatively short time of death gives the test denoting the presence of choline or some substance from which choline is easily dissociable. We have been unsuccessful in obtaining the test in fluids obtained during life, even in the cases of general paralysis. A large number of papers have appeared on this subject, and the points under dispute are (1) the reliability of the tests employed; and (2) whether the substance present is really choline or some other similar or even dissimilar product of the cleavage of the complex phosphatide molecules. The questions are difficult to settle owing to the small quantity of the substance present in the fluid, but it would appear that, although choline may be split off from the phosphatide molecule during the course of active degeneration of nervous tissues, it cannot exist as such in the alkaline cerebro-spinal fluid. However, as our knowledge regarding the exact chemical composition of the complex substances of nervous structures increases, we may be able to ascertain the nature of the cleavage products of these substances in nervous degeneration.

I may remark that the potassium salts which are present in relatively so large amount in brain tissue, and which the experiments of Macdonald would suggest as being increased in the fluid in cases of degenerative destruction of the nervous system, are not appreciably altered in amount.² This does not prove, however, that the potassium salts do not pass into the cerebro-spinal fluid and blood and that they are not increased, for it is extremely difficult to estimate differences

² Myers has estimated the potassium salts in the cerebro-spinal fluid in a number of general paralytics and non-paralytics with the following result. *General paralytics* (13 cases).—Average 0.038 per cent. KCl. (Highest, 0.064 per cent.; lowest, 0.027 per cent. KCl.) *Non-paralytics* (4 cases).—Average 0.033 per cent. KCl. (Highest, 0.039 per cent.; lowest 0.027 per cent. KCl.) These results were obtained from 10 cubic centimetres of cerebro-spinal fluid in each case, and it was deemed advisable, in repeating the work, to make determinations on appreciable quantities of fluid from two or three cases instead of on smaller quantities from each case. I have therefore examined larger quantities of cerebro-spinal fluid obtained by adding together the fluids from several cases of dementia præcox and general paralysis with the following results:—

<i>Dementia Præcox.</i>	<i>General Paralysis.</i>
1. 27.5 c.c. 0.033 per cent. KCl.	1. 40 c.c. 0.038 per cent. KCl.
2. 27.5 c.c. 0.038 " "	2.* 40 c.c. 0.034 " "
3. 26.0 c.c. 0.030 " "	Average 0.036 " "
Average 0.033 " "	

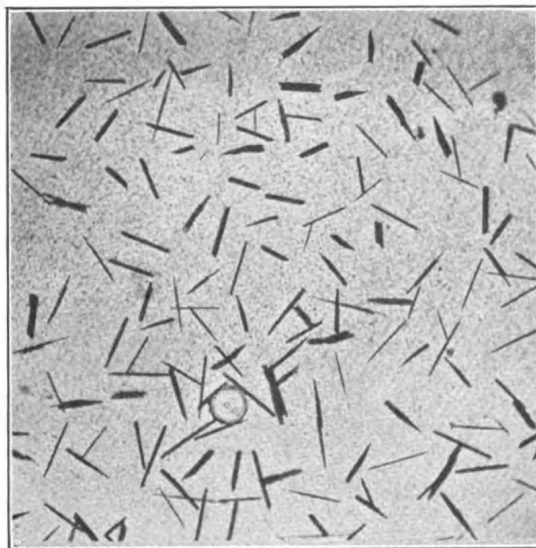
All fluids used in this instance gave a positive Wassermann reaction.

where such small quantities have to be dealt with. Moreover, seeing that the quantity of potassium salts is approximately the same as the blood, any increase would tend to diffuse.

There is little more to be said about the chemical alterations, but I will throw on the screen an outline of a rough method for the chemical examination of the cerebro-spinal fluid. Ten cubic centimetres of the centrifuged fluid, after examination for cells has been made, are taken and rendered faintly acid with acetic acid. Three cubic centimetres of absolute alcohol are added and the whole gently heated on

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FIG. 10.



Photomicrograph of crystals of choline periodide obtained from a small quantity of the cerebro-spinal fluid of a non-paralytic case, taken a few hours after death.

a water bath for 15 minutes. After standing overnight it is again warmed and filtered. The amount of protein can be approximated at sight or weighed on a tarred filter-paper or Gooch crucible, the amount of ash being subtracted from the total weight of protein. The filtrate is rapidly evaporated to dryness at a low temperature, the residue is moistened, and a smear transferred on the end of a glass rod to a slide, and one drop of a saturated solution of iodine in 10 per cent. potassium iodide is added. The mixture is now watched under the microscope, *when, if choline is present, brownish-black rectangular plates of choline periodide will be formed.* (Fig. 10.) The moisture is

removed from the residue by evaporation, and another extraction with absolute alcohol is made. The filtered extract is evaporated to *dryness* and extracted with hot chloroform. The volume of chloroform is reduced to about 2 cubic centimetres and the presence of cholesterol detected by Liebermann's test which is thus carried out. (Add to chloroform solution a few drops of acetic anhydride, then (add concentrated sulphuric acid drop by drop. After a time a rose colouration of the acid, and a violet colouration of the chloroform turning to blue, then green, indicate the presence of cholesterol.)

The test for sugar can be performed on one or more cubic centimetres of the original fluid, and Noguchi's and other confirmatory tests may be made on any remaining fluid. Many observations have been made based upon the examination of fluids obtained after death; I have found, however, that within a very short time after death the composition of the fluid so alters that the results obtained are useless and misleading.

Experiments show that if micro-organisms enter the sub-arachnoid space they rapidly multiply in the cerebro-spinal fluid and lead to a general colonisation. We may suppose that the micro-organisms invade the perivascular lymphatics and set up an inflammatory reaction therein, which if it does not localise the spread will eventually lead to the organisms getting into the subarachnoid space and by the movement of the cerebro-spinal fluid lead to a general infection of the membranes.

PATHOLOGICAL CONDITIONS.

Time will not permit me to do more than summarise the abnormal conditions of the cerebro-spinal fluid as a whole, and I will throw on the screen a table illustrating the principal features occurring in pathological conditions. In this table you will observe that I have made four groups, and I shall dwell more especially upon those points upon which my assistants at Claybury and myself have chiefly worked, therefore about which I have special knowledge. (Table II.)

SLEEPING SICKNESS, SYPHILIS, AND PARASYPHILIS.

The work in which I have been especially engaged has been the investigation of the pathological conditions met with in sleeping sickness, in syphilis, and in parasyphilis, pathological conditions in which there are many points of similarity. The meninges and perivascular lymphatics in all three of these diseases are characterised by a lymphocyte and plasma cell infiltration, and by a hyperplasia of the neuroglia cells indicative of a chronic inflammatory pro-

cess, due in all probability in each case to toxic irritation. In all three of these diseases the cerebro-spinal fluid contains a large number of mononuclear cells—leucocytes.

I shall have occasion later to demonstrate other points in connexion with the cerebro-spinal fluid in these diseases. You will observe how similar is the appearance of the perivascular lymphatics of sleeping sickness, general paralysis, and syphilis. But the diseases in question present many patho-

TABLE II.—*Abnormal Conditions of the Cerebro-spinal Fluid.*

<p>I. <i>Cytological examination</i>.—Normal fluid is practically free from cells. In pathological conditions an estimation is made of the type and number of cells.</p>	<p>1. <i>Polynuclear leucocytosis</i> generally indicates microbial invasion of the subarachnoid space by some organism other than the tubercle bacillus; but polynuclear cytois may accompany lymphocytosis in a certain proportion of cases of tuberculous meningitis.</p> <p>2. <i>Mononuclear leucocytosis</i>.—Whereas polynuclear leucocytosis points to an acute inflammatory affection of the meninges, mononuclear leucocytosis indicates a chronic condition. It occurs almost invariably in syphilis of the central nervous system, general paralysis, tabes dorsalis, tuberculous meningitis, and sleeping sickness. It has been found in other conditions—e.g., herpes zoster, acute poliomyelitis, mumps, lymphatic leukaemia, chloroma, and some cases of cerebral tumour. Mononuclears may also replace the polymorphs in the later stages of microbial infection.</p>
<p>II. <i>Bacteriological examination</i>. (a) Staining the centrifuged deposit. (b) Cultural methods. (c) Inoculation.</p>	<p>The most important organisms found are: pneumococcus, streptococcus, bacillus tuberculosus, diplococcus intracellularis causing meningitis. Various other micro-organisms, together with pneumococcus, pneumo-bacillus streptococcus, and staphylococcus may, as a result of secondary or terminal infection, invade the subarachnoid space.</p>
<p>III. <i>Protozoal examination</i>. (a) Staining the centrifuged deposit. (b) Examination of a hanging drop. (c) Inoculation.</p>	<p>The only protozoon met with constantly in the disease which it causes is the <i>Tryp. gambiense</i>. Only once has the <i>Treponema pallidum</i> been found.</p>
<p>IV. <i>Biochemical</i>.</p>	<p>The Wassermann reaction of the blood serum combined with that of the cerebro-spinal fluid.</p>

logical differences which would explain the different clinical phenomena. Let me first refer to sleeping sickness, a disease caused by the *Tryp. gambiense*. Whether this chronic irritation of the lymphatics is due to toxins produced by the invasion of the blood and lymphatic system of the body generally or to the presence of the organism in the cerebro-spinal fluid, is still a matter open to discussion, but I think from the examination of the brains of over 30 cases

of this disease that there is a parallelism between the somnolence or drowsy stupor which is the characteristic feature of this disease and the degree and intensity of this perivascular lymphatic cell infiltration. I would attribute this to the interference with the circulation of the ambient fluid of the neurons, whereby they suffer from an insufficiency of oxygen. It cannot be explained by an interference with the blood circulation, for the anæmia is not intense enough; it cannot be explained either by degenerative changes in the nerve cells, such as we find in general paralysis, for in those cases, and I may say they were few, in which a secondary microbial invasion by diplococci, streptococci, or staphylococci had not taken place, the brain presented a normal appearance to the naked eye. There was no wasting, and microscopical examination did not reveal sufficient changes in the nerve cells to account for the symptoms manifested during life. Europeans who have suffered with sleeping sickness, and a Congo native speaking English well who died under my care in Charing Cross Hospital, could be roused from their drowsy lethargy to answer questions rationally—a very different condition to that of general paralysis, where the auto-critical faculty is almost invariably affected. The drowsy lethargy of this disease I attribute then to the failure of the oxygen supply to the cells of the cortex.

We can readily understand how this could be effected, if the fluid which circulates in the perivascular lymphatics is the ambient fluid that takes oxygen from the blood to hand it over to the nerve cells; this progressive, universal, and intense inflammatory state of the perivascular lymphatics would interfere with its flow and lead to deficient oxygen supply. Moreover, there is a vicious circle established, for the more these lymphatics become obstructed by the actively growing young cells the more the oxygen that may be in the fluid will be snapped up by them and the less will be at the disposal of the nerve cells. Consequently, the oxygen supply necessary for functional activity of the nerve cells becomes progressively less and the drowsy stupor deepens proportionately.

The experiments of Verworn, upon which I have not now time to dwell, prove the importance of oxygen storage by the nerve cells and the necessity of its supply for functional activity. Moreover, the experiments of Baeyer and Winterstein point to the fact that narcotics act by an interference with the capacity of the cell to take up oxygen, whereas normal sleep is a habit on the part of the cell of storing rather than of using oxygen.

In widespread generalised syphilitic meningitis and perivascularitis a drowsy stupor is a frequent symptom, but I attribute this in a measure to the interference with the escape of fluid from the ventricles of the brain in some cases, but in others, more particularly to the widespread

obliterative endarteritis affecting the small as well as the large vessels, thus producing a generalised anæmia.

In general paralysis the perivascularitis may be very intense, but never so intense as in sleeping sickness. The dementia, which is *the* characteristic of the former disease, is proportional to the atrophy and wasting of the cortical substance, a condition which is not met with in either sleeping sickness or syphilitic brain disease. It is a primary decay of the neurons with secondary and proportional vascular changes, whereas in syphilitic brain disease the wasting and degeneration of the neurons occur in foci as a result of vascular occlusion from endarteritis or the consequent thrombosis; the symptoms are obtrusive and coarse and occur in sudden spells, whereas in general paralysis, leaving aside the seizures which may occur, the disease is insidious, continuous, and progressive.

In all these diseases, as I have said before, there is a mononuclear leucocytosis of the cerebro-spinal fluid; therefore, diagnosis by cytological methods will not suffice. There is generally also a hypertension of the cerebro-spinal fluid. Now we can leave out a consideration of sleeping sickness, for no one would diagnose that without finding the *Tryp. gambiense* in the cerebro-spinal fluid, lymphatic glands, or blood. The important point is the differential diagnosis of syphilis from parasyphilis of the nervous system. Of the importance of this one cannot be too emphatic, for whereas syphilis of the nervous system is curable or, at any rate, benefited by mercurial treatment and administration of iodides, it is doubtful whether parasyphilis is ever cured or even benefited by this treatment, and in some cases it positively does harm. And this leads me to say that I do not regard the diphtheroid organisms described by Ford-Robertson as the organism of tabes and general paralysis as in *any* way a specific organism of this disease. My assistant, Dr. J. P. Candler, made a special study of this subject, and we have never been able to find the bacillus in the cerebro-spinal fluid, and only on one occasion was it seen in the blood, although we have examined a very large number of specimens. I think, therefore, we can leave it out of account as a means of diagnosis. Now I come to a very important method of distinguishing syphilitic disease of the nervous system from parasyphilis—I refer to the Wassermann reaction.

THE WASSERMANN REACTION.

The Wassermann reaction since its introduction has had many modifications, but it is a general opinion that, although the theory upon which Wassermann based his method is wrong, yet empirically, although the method is more tedious and more difficult of application, it is nevertheless more reliable in its results; and Dr.

Candler and Dr. J. Henderson Smith of the Lister Institute have relied upon this method entirely for the results which I shall place before you. The reaction is as follows. A rabbit is immunised against the blood of the ox—that is to say, several injections of washed ox corpuscles are injected into the rabbit. The serum of this animal has then the power of dissolving the red corpuscles of the ox. This is owing to the presence of two substances—the complement, which is thermolabile, and the amboceptor, which is thermostable. If this serum is heated to 56° C. for 30 minutes it will no longer dissolve washed ox corpuscles, but if some normal guinea-pig serum be added the corpuscles are dissolved. This is due to the fact that the thermolabile substance—the complement—has been added, and in conjunction with the thermostable amboceptor has caused hæmolysis.

The serum or cerebro-spinal fluid to be examined is mixed in varying dilutions with a watery or alcoholic solution of the liver of a syphilitic fœtus; a small amount of guinea-pig serum is then added, and the total volume made up to 2 cubic centimetres with saline solution. A series of tubes containing these mixed solutions is placed in the incubator at 37° C. for one hour and the sensitised ox corpuscles are added. The mixtures are again placed in the incubator for two hours at 37° C., then taken out and put on ice overnight. The next morning the amount of hæmolysis in each tube is observed. A control experiment, using normal serum or cerebro-spinal fluid, should be made at the same time. A positive reaction is obtained when the blood or cerebro-spinal fluid causes fixation of the complement of the guinea-pig serum and hæmolysis is prevented.

It has been found that extract of guinea-pig heart, of human heart, soaps, and lecithins may replace the extract of syphilitic liver in this reaction. Consequently, the idea of the antigen and antibody theory has been abandoned. Still, it is everywhere accepted that the reaction is a most reliable aid to diagnosis.

I have purposely omitted to give the details and precautions necessary for the satisfactory carrying out of this reaction as they are given fully by Henderson Smith and Candler. They have recently examined the cerebro-spinal fluid of 127 cases of various forms of insanity. Of this number, 64 were cases of general paralysis, and in 59, or 92·1 per cent., a positive result was obtained. Of these 59 cases, 21 have since died, and the clinical diagnosis of general paralysis has been confirmed by the post-mortem investigations. Fluids from 63 cases not suffering from general paralysis were also examined, and in no single instance was a positive reaction obtained. A few of these cases have since died, but none showed at necropsy any evidence of general paralysis. 17 out of the 21 cases of

general paralysis above referred to, which came to the post-mortem table, showed before death an excess of lymphocytes in the cerebro-spinal fluid.

The following table shows the results obtained by Henderson Smith and Candler in general paralysis and tabes, as compared with those collected from the literature.

TABLE III.—*Comparison of Results obtained by Henderson Smith and Candler with those collected from the Literature.*

—	Cerebro-spinal fluid.	Serum.
<i>General paralysis.</i>		
In literature	352 cases, 309 positive; that is, 87.7 per cent.	285 cases, 247 positive; that is, 86.6 per cent.
Henderson Smith and Candler's cases ...	64 cases, 59 positive; that is, 92.1 per cent.	10 cases, 9 positive; that is, 90.0 per cent.
<i>Tabes dorsalis.</i>		
In literature	112 cases, 57 positive; that is, 50.8 per cent.	176 cases, 125 positive; that is, 71.0 per cent.

Plaut, who was the first to adopt the Wassermann test for the cerebro-spinal fluid, obtained as high a percentage as 90 out of 91 cases, and in every case the serum was positive. He points to the fact that the Wassermann reaction may occasionally be obtained before there is any cell increase in the fluid, although this is the exception according to our experience, yet in one of the cases the reaction was only obtained a few days before death. The diagnosis was confirmed post mortem, macroscopically and microscopically; the cerebro spinal fluid was withdrawn two hours after death and specimens of lateral ventricle fluid and serum from this case gave strong positive reactions. In this instance, then, although the fluid eventually became positive, it was still negative until a short time before death, when the disease was far advanced. In one of the cases the fluid remained negative throughout. It is unusual to obtain a positive reaction of the cerebro-spinal fluid in syphilis of the central nervous system, although the fluid may contain a large number of lymphocytes. There does not, then, seem to be any correlation between the lymphocytosis *per se* and the presence of the body which gives the reaction. But although syphilis of the nervous system is not accompanied by the reaction in the cerebro-spinal fluid the serum, unless the patient is under active treatment, always gives the reaction. The explanation of this is somewhat difficult. Concerning the chemistry of the Wassermann reaction I have found that a fluid giving a positive reaction fails to do so after the separation of the protein fraction. Sachs concludes that the substance is a globulin and Noguchi has come to

the conclusion that the substance in the fluid causing the reaction is attached to the eu-globulin, from which it cannot be separated by solvents. In respect to the manner in which this arises in the cerebro-spinal fluid several suggestions offer themselves, one being that it is a transudation from the blood. If it were so we should expect to find it in cerebral syphilis, but as a rule this is not the case. Inasmuch as I have shown that the cerebro-spinal fluid is secreted by the choroid plexus I was naturally led to make a comparative examination of this structure in general paralysis and other diseases, but although the choroid plexus in general paralysis as compared with other diseases of corresponding age showed more frequently cystic degeneration and denudation of the choroidal epithelium, still I was unable to associate so far the two facts. A positive reaction by the Wassermann method is not necessarily associated with lymphocytosis, neither is lymphocytosis even with a positive serum reaction necessarily associated with a positive reaction of the cerebro-spinal fluid. It may be said that a positive reaction of the cerebro-spinal fluid strongly points to a parasymphilitic affection. Time will not permit me to discuss certain theories which I have put forward in explanation of parasymphilis and the presence in the cerebro-spinal fluid of a body upon which the fixation of the complement depends, but I have dealt with the subject in the Morison Lectures of 1909. I will be content with giving three striking examples out of a number of the value of this reaction.

CASES SHOWING THE APPLICATION OF THE TEST.

1. My attention was called to a case in one of the London county asylums of a woman with double optic neuritis, vomiting, and headache. I had her transferred to my care at Charing Cross Hospital, and on examination Mr. E. T. Collins found five dioptries of swelling in each disc. The cerebro-spinal fluid contained an abundance of lymphocytes but the Wassermann reaction was negative. After treatment with mercurial inunction the swelling of the discs rapidly subsided, the vomiting and headache ceased, and she was able to read small print, whereas formerly she could not read large print. She was subsequently discharged apparently cured.

2. The condition of a patient in one of the London county asylums improved so much that the medical officers were doubtful as to whether he was a general paralytic. The Wassermann test was made on the cerebro-spinal fluid with a positive result. I expressed the opinion that it was certainly a case of general paralysis and maintained that the test was not likely to be wrong. He still continued to improve and his discharge was contemplated, but the next time I visited the asylum my prediction was confirmed. He had

had several seizures and within three months he died, and the examination of the brain left no doubt as to the correctness of the diagnosis.

3. A woman, aged 34 years, was admitted to Charing Cross Hospital under my care, said to be suffering from tabes. There were no signs of syphilis on the body. Her youngest child was aged 4 years. Fifteen months previously she had had a seven months stillborn child. Four months ago she suffered with numbness in the legs, of which she took little notice; then she had double vision and tingling in the feet and legs. For the past 14 days she had suffered with a girdle sensation. She now complained of lancinating pains extending from the back down both legs, unsteadiness in gait and station, a feeling of the soles as if walking on cork, and pain and cramp in the muscles of the legs. The pupils were unequal and reacted sluggishly to light and to accommodation, the knee-jerks were absent, there were patches of anæsthesia on the legs, and a belt of thoracic anæsthesia with girdle sensation. After inquiring into the history and finding that she had suffered with headache and squint, that the knee-jerks, which were absent on admission, had returned a few days later, I concluded that this woman, with a probable duration of infection of less than four years, was suffering from pseudo-tabes, the result of syphilitic meningitis, especially as she told me that she had suffered with a slight stiffness of the neck. I then obtained Kernig's sign. The cerebro-spinal fluid showed 390 lymphocytes per cubic millimetre—an enormous number for tabes dorsalis; this large number could only be accounted for by a widespread active gummatous meningitis. She was placed on mercurial inunction, and within a fortnight the lymphocytes had fallen to 70 per cubic millimetre and the fluid gave a negative Wassermann reaction. Unfortunately, the blood was not tested on this or future occasions. A fortnight later the cerebro-spinal fluid was examined and only 20 lymphocytes per cubic millimetre were found, the patient being almost well. A fortnight later there were no lymphocytes and the fluid was still negative to the reaction. The pains, anæsthesia, and unsteadiness had entirely disappeared and the patient was quite well. Over a year has elapsed and the patient is still quite well, but there is no guarantee that she may not have a recrudescence of symptoms, for my experience has taught me that if once the contagion invades the subarachnoid space producing a diffuse meningitis, symptoms of a latent affection becoming once more active may supervene at any period after.

In conclusion, I wish to acknowledge my indebtedness to my assistants, Dr. Candler and Mr. Sydney Mann, for the invaluable help they have afforded me in conducting these researches and investigations.

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The Huxley Lecture
ON
**THE HEREDITARY ASPECTS OF NERVOUS
AND MENTAL DISEASES.**

*Delivered at the Opening of the Winter Session at Charing
Cross Hospital on Oct. 3rd, 1910,*

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MR. CHAIRMAN,—Permit me to thank you and my colleagues of Charing Cross Hospital Medical School most cordially for the great honour conferred upon me by the request to deliver the Huxley Lecture this year. When I look back on my distinguished predecessors I feel that, with this honour, there is a great responsibility, for it is not an easy task for me to deliver a lecture worthy of the occasion; and I felt, therefore, some difficulty in the selection of a subject. I was, however, guided in my selection of the hereditary aspect of nervous and mental diseases by the following facts. Heredity is a subject that the master mind of Huxley illuminated in several of his essays, and it is fundamental in the study of the Origin of Species and Natural Selection, which he did so much to forward. Next, recent developments in our knowledge of the subject of heredity owing to the labours of Galton, Pearson, and their followers in the study of biometrics, and Bateson and his followers in Mendelism, have aroused the keenest interest in the subject of human inheritance, not only in the medical profession, but in the thinking and intellectual portion of the nation. Another reason was that none of the illustrious lecturers in the past have dealt with the subject of heredity in relation to disease. Lastly, it is a subject to which I have recently devoted a large amount of attention in the study of the causation of nervous and mental diseases, and more especially the relation of heredity to various forms of insanity. The wealth of material in the London County

Asylums has permitted a biometric investigation in a novel manner. The subject is one of national importance and interest, and it affects many social and legislative questions. The interest taken by the general public in the question of heredity is a sign of social progress. People are recognising the truth of Thomson's saying, "The present is the child of the past; our start in life is no haphazard affair, but is vigorously determined by our parentage and ancestry; all kinds of inborn characteristics may be transmitted from generation to generation."

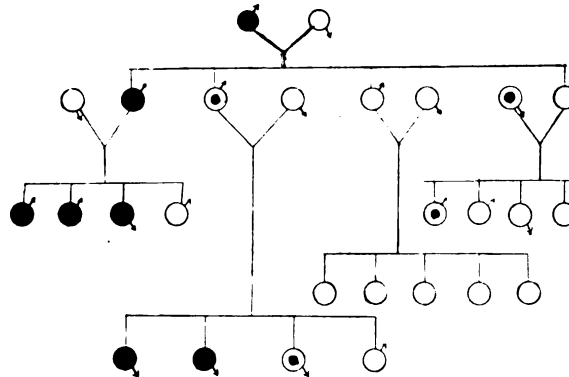
DOCTRINES OF HEREDITY.

Fifty years have elapsed since Huxley wrote an essay on the Origin of Species in the *Westminster Review*, and the doctrine of Natural Selection which he upheld with such remarkable force remains unshaken and unshakable, but mutation or discontinuous variation has replaced in great measure the continuous accumulation of small differences to which Darwin attributed so much importance in evolution; and it is interesting to note that Huxley in this same essay said, "Mr. Darwin's position might, we think, have been even stronger than it is, if he had not embarrassed himself with the aphorism, *Natura non facit saltum*, which turns up so often in its pages. We believe that nature does make jumps now and then, and a recognition of the fact is of no small importance in disposing of many minor objections to the doctrine of transmission." Huxley cites the case of the Ancon sheep, also an interesting pedigree of polydactylism narrated by Réaumur. I will show a diagram (Fig. 1) illustrating this condition in three generations. Réaumur narrates this case only as far as the third generation, and Huxley remarks: "Certainly it would have been a curious thing if we could have traced this matter any further; had the cousins intermarried, a six-fingered variety of the human race might have been set up." In the light of the Mendelian law of gametic segregation even this would not be necessary, for a variation is "not swamped out." But sexual selection would tend against the perpetuation of this variation, which does not serve a useful purpose, nor is it an ornament. Huxley in another essay on Hereditary Transmission and Variation refers to the different product of crossing a stallion with a she ass, and a male donkey with a mare. "Here you see is a most curious thing; you take exactly the same elements, Ass and Horse, but you combine the sexes in a different manner and the result is modified accordingly. Here, then, is one and perhaps a necessary cause of variation." There is in these instances a prepotency of the male in certain physical characters; for on the one hand when the donkey is the sire a mule is produced with the head, ears, and voice resembling that

animal, when on the other hand the horse is the sire a hinny is the product, with head, ears, legs, and voice like the horse.

Again quoting Huxley: "A certain amount of variation is the necessary result of sexual propagation itself; for inasmuch as the thing propagated proceeds from two organisms of different sexes and temperaments, and as the offspring has to be either of the one sex or the other, it is quite clear it cannot be a diagonal of the two or it would be no sex at all; it cannot be an exact intermediate form between that of each of its parents; it must deviate either to one side or the other. You will have noticed how very often it may happen that the son shall exhibit the maternal type of character, or the daughter possess the characteristics of the father's family."

FIG. 1.



Polydactylism. The circles with black centre indicate partial polydactylism. The black circles are complete polydactylism. The chart is very suggestive of Mendelism.

The law of ancestral heredity of Galton supposes that every ancestor of a particular individual contributed its quota to the heritable qualities of the individual. The law also states that the average amount of resemblance between an individual and any particular ancestor is capable of definite numerical expression. Thus the mean amount of correlation between (1) the two parents and the offspring; (2) the four grandparents and that offspring; and (3) the great-grandparents and that offspring, and so on backwards in the ancestral lineage, is believed to diminish in a geometrical series one-half, one-quarter, one-eighth, which is the same for all organisms and their characters. Pearson represents a more rapidly diminishing series: (1) for the two parents, 0.6244; for the grandparents, 0.1988; for the great-grandparents, 0.0630, &c. We thus have a mosaic of ancestral characters.

It is quite possible that the above represents correctly the average total contributions of ancestors when applied to the race as a whole, but it cannot be universally applied to individuals, for, according to Mendel's theory of inheritance, certain ancestors may contribute nothing to the constitution of certain offspring in respect to certain characters. Moreover, as Maudsley truly says, it is a conclusion which, however true on the average of such simple characters as height, is manifestly not true of individual cases. Anyone selecting for observation different characters—e.g., noses or ears—can see plainly the nose may be like the father's or the mother's, or perhaps one of the grandparent's or further back. This fact was well known to the ancients, and, according to modern ideas of heredity, there is not much to be said against the teaching of Lucretius. "Sometimes, too, the children may spring up like the grandfathers, and often resemble the forms of their grandfather's fathers, *because the parents often keep concealed in their bodies many first beginnings mixed in many ways, which first proceeding from the original stock, one father hands down to the next father and then proceeding from these, Venus produces forms after a manifold chance and repeats not only the features but the voice and hair of forefathers, and the female sex equally springs from the father's seed and males go forth equally from the mother's body, since these distinctions no more proceed from the fixed seed of one or other parent than our face and bodies and limbs. Again, we perceive that the mind is begotten along with the body and grows up together with it, and grows old along with it.*" The individuality of every human being depends upon the mingled natures of two separate parents, and Goethe poetically refers to his own hereditary endowments in the following lines:—

" Vom Vater hab ich die Statur,
Des Lebens ernstes Führen,
Vom Mütterchen die Frohnatur
Und Lust zu fabulieren."

According to the Mendelian doctrine of dominant and recessive, the corresponding character of the second parent always exists in the offspring side by side with the character which finds expression, only the former, termed recessive, is obscured by the latter, the dominant. This is the explanation of a characteristic feature of a particular grandparent which was not visible in the parent reappearing in the child (*vide* Fig. 1). It also accounts for those heritable diseases and abnormalities which are transmitted by the females in ancestry and appear in the males—e.g., hæmophilia, Daltonism, pseudo-hypertrophic paralysis. As it passes from a father through a daughter to a grandson, and so on, it must be latent in the germ cells (concealed in the body) though for some obscure reason it has not found expression. In fact, non-expression of a disease does not necessarily

imply non-inheritance of a disease, rather a predisposition to disease. It is well known that a hereditary tendency to nervous disease may have different expressions in successive generations—e.g., insanity and epilepsy; the hereditary transmission of nervous or mental disease is rather of the nature of a neuropathic tendency, the character of the disease being largely determined by the exciting cause. I have not time to discuss further the large question of Mendelism in relation to human inheritance, so far I have not met with any cases in entire support thereof, in the study of the hereditary aspect of nervous and mental disease, but, as pointed out by Professor Bateson, there are many reasons why it has not been found applicable. Of its enormous importance to biology and heredity there can be no question; even Professor Pearson, its most strenuous opponent, said, "The importance of Mendel's work and his followers lies in the observation of segregation"—this great fact holds whether Mendelism in its simple form remains or not.

THE RARER NERVOUS DISEASES AND HEREDITY.

Among the rarer nervous diseases in which it is generally recognised that heredity plays an important part may be mentioned myotonia congenita, pseudo-hypertrophic paralysis, progressive muscular dystrophy (especially the Landouzy-Dejerine facio-scapular type), the neuritic type of progressive muscular atrophy, hereditary ataxia, Huntington's chorea, and family periodic paralysis. In nearly all the recorded cases of myotonia congenita (Thomsen's disease) the disorder has existed in several relatives of the patient, generally in one of the parents and in the patient's brothers, sisters, and children. More than 20 cases of the kind occurred in the family of Dr. Thomsen in four generations. It is to him that we owe the first accurate description. As in Huntington's chorea (a remarkable pedigree of which I shall show you), other neuroses frequently occur in the family tree. Many of Thomsen's relatives were affected mentally. Sir William Gowers in the recent discussion on heredity in relation to disease at the Royal Society of Medicine referred to the frequency with which pseudo-hypertrophic paralysis is hereditary; he likewise pointed out that the disease is characterised by sex limitation, and cited a very remarkable case, in which the disease, although not affecting the females, passed through to the males in several successive generations; there were two families and probably both originated in the same stock. Again, he referred to a remarkable case of facio-scapulo-humeral atrophy (Landouzy-Dejerine type) which could be traced for six generations.

Family periodic paralysis is a rare disease with a well-marked hereditary tendency. It is characterised by periodic

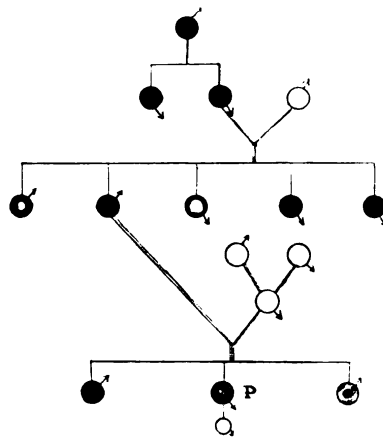
attacks of more or less extensive flaccid motor paralysis with a loss of electrical excitability in the paralysed muscles and of the reflexes, but without sensory affection or disturbance of consciousness. Between the attacks the patient is well. In a family recorded by E. W. Taylor there were 11 cases in one generation; in the family of a patient of Goldflam there were 11 cases on the maternal side, and Holtzapfel observed 17 cases in four generations. The disease may be transmitted indifferently through the father or the mother, although occasionally there has been limitation of transmission to the same sex. As in other diseases with a similar hereditary character, individual cases may occur in which there is no family history of the disease. A remarkable case of neuritic progressive muscular atrophy, showing that it might be of a hereditary character, was reported by Herringham; the disease was transmitted by females, but only males were affected. The disease, however, may be transmitted by both males and females, and both sexes are affected.

Friedreich's disease, although called hereditary ataxia, is seldom directly hereditary—it is a familial disease. Several families and several isolated cases have come under my observation, but in the isolated cases no family history of the disease in ascendants was found, nor was it in the two cases affecting a number of members of the family; in one of these there was a history of consanguinity, the parents of this family of hereditary ataxia cases being first cousins. A remarkable pedigree of hereditary ataxia worked out by Sanger Brown, however, shows the disease occurring in five generations of a family. Gordon Holmes states that Schoenborn found a family incidence in 114 of the 200 cases he analysed. Yet in a not inconsiderable number of recorded cases the same disease occurred in the ascendants or in the collateral lines. It may be transmitted through either males or females. Occasionally there is not direct heredity, but the disease occurs in families in which there seems to be a proclivity to spinal disease; for instance, a pedigree which I obtained at Darenth Asylum showed this relationship; moreover, occasionally, as this pedigree showed, it may be associated with idiocy. Nolan and Pritzsche have recorded cases associated with progressive idiocy.

I will now pass on to the consideration of a disease which I have met with occasionally in the asylums—viz., Huntington's chorea, in which a direct heredity has been found practically in all the cases studied. The accompanying pedigree (Fig. 2) is a striking one kindly furnished to me by Dr. C. H. Bond of Long Grove Asylum, under whose care is the patient of the fourth generation. Huntington, who first gave a complete picture of the disease, and after whom it was named Huntington's chorea, remarks: "If one or both of the parents have shown manifestations of a serious nature, one or more of the offspring almost invari-

ably suffer from the disease if they live to adult life, but if by any chance these children get through life without it, the thread is broken and the grandchildren or great grandchildren may rest assured that they are free from the disease. Unstable and whimsical as the disease may be in other respects, in this it is firm; it never skips a generation to manifest itself in another; as soon as it has yielded its claims it never regains them." Huntington also remarks upon the presence of the nervous temperament in all, or nearly all, of the families in which there is the taint of this disease, and says "that nervous excitement to a marked degree almost invariably attends upon every disease these persons may

FIG. 2.



Paternal great-grandfather suffered with chorea—also paternal grand-mother and sister. Two paternal aunts and father suffered with chorea and died in asylums or infirmary—brother and sister physically unsound. P., the patient chorea and insane, one brother in asylum and one died. It will be observed that the maternal side is quite free from any taint.

suffer from, although they may not in health be over nervous." Heilbronner states that there is a tendency in successive generations for the onset of the disease to be delayed, and Wollenberg has shown as this pedigree very clearly indicates, that choreic heredity in some cases may be transformed into other neuroses—i.e., epilepsy, imbecility, paranoia, grave hysteria, &c. Wollenberg has collected statistics of 128 cases in 22 families, of which 74 were in men and 54 in women, thus confirming Huntington's statement that it is more common in men than in women. Again, it was observed by Huntington that "the tendency to insanity, and sometimes that form of insanity which leads to suicide, is marked, and the mental condition usually termi-

nated in dementia." In several cases a microscopic examination revealed a marked neuronie atrophy, with some neuroglia hyperplasia of both the frontal lobes, including also the central convolutions. Changes in the Betz cells have been described which might be correlated with the motor disorder manifested during life. I have observed changes of an abiotrophic character in the Betz cells in paramyoclonus multiplex affecting four members of a family; an uncle was an epileptic, but no other ancestral defect was discovered.

These forms of nervous disease are usually due to characteristic morphological defects, and for the most part are best explained by germinal defects in the specific vitality of groups of muscles or systems of neurons whereby they waste prematurely. Sir William Gowers has introduced the term of abiotrophy for this condition. From a practical point of view on account of their rarity abiotrophies are of little importance as compared with insanity and epilepsy, to which I shall now direct your attention.

EPILEPSY.

With regard to epilepsy I feel convinced from my own observations and experience that Sir William Gowers is correct when he asserts that there are few diseases in the production of which inheritance has a more marked influence and the traceable influence is always far less than that which exists. Voisin, Ferè, Nothnagel, Dana, Peterson, and Aldren Turner express similar opinions.

In the discussion of the subject of heredity and disease Sir William Gowers said: "In my own enquiries into the heredity of epilepsy I have limited myself to these two maladies, epilepsy and insanity. Heredity was ascertained in 39 per cent. of 1193 males and 43 per cent. of 1207 females. When epilepsy itself occurred in a parent it was the father who was epileptic in 49 per cent. and the mother in 51 per cent. The cases with insanity in a parent are only one-third the number compared with parental epilepsy. Of the cases with parental insanity the father was insane in 37 per cent. and the mother in 63 per cent. One effect of heredity is to increase the female cases. When it was absent the excess of males amounted to 4 per cent., but in cases of heredity the same excess was presented by females. This is partly due to the fact that inheritance is more frequently from the mother's side by 17 per cent., and that the females are in excess by 18 per cent." These facts (obtained by Sir William Gowers) are in many ways in striking conformity with the results obtained by my investigation of insane relatives in the London county asylums as regards certain types of insanity which I shall shortly relate. Moreover, I have observed that a similar heredity occurs in a considerable number of cases of insane epileptics, at least

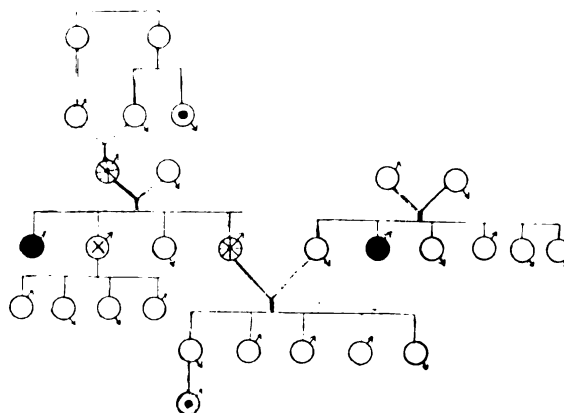
20 per cent. Spratling from his large experience at Craig Colony gives 16 per cent. of similar heredity.

HEREDITARY CAUSATION OF INSANITY.

There are a few alienist physicians who do not have a strong belief in the hereditary causation of insanity, and my esteemed colleague, Dr. C. A. Mercier, at the discussion on heredity said: "When we are confronted with the percentage of persons among whose near relatives insanity is known to exist we cannot fail to be impressed with two remarkable facts, first how relatively small their percentage is, and second, that the statistics, even if taken at their face value, do not purport to be anything but an *enumeratio simplex* and cannot be made the basis of any valid conclusion until they are compared with similar statistics of the percentage of insane relatives among the sane." He also stated that the published statistics are of no value at all for any practical or scientific purpose. With this I would entirely agree, but in taking statistics among the sane population we should find that insanity and epilepsy would often occur in families where there are neuroses, eccentricity, and even genius, all of which were variations from the normal average of the species. I have endeavoured to ascertain what is the proportion of insane, feeble-minded, and epileptic members occurring in the pedigrees of my hospital patients; and I am greatly indebted to my house physician, Dr. W. R. Thomas, for the careful and painstaking way in which he has obtained information from the friends. In 32 pedigrees, which would include about 1000 living representative and 250 dead individuals, there were eight who had been in asylums and in eight others fits were chronicled. In no case was either parent of the patient insane or epileptic. Two of the pedigrees furnished most of the cases. (Fig. 6.) One was a patient suffering from neurasthenia in which there were, besides insanity and epilepsy, migraine, hysteria, deaf-mutism, and imbecility, and the other a patient with exophthalmic goitre with several neuropathic members in the stock. I must confess that had I to prove my case by comparing the pedigrees thus obtained with some pedigrees obtained at the London County Asylums and Imbecile Asylum at Leavesden (20 non-selected pedigrees were kindly taken for me by Dr. F. A. Elkins and his medical officers), I should not have a very strong case, for in a very considerable proportion of the cases admitted to these asylums interrogation of the friends elicits no evidence of insanity on either side. Yet most alienist physicians would not agree with Dr. Mercier in casting doubt upon the importance of heredity in the production of insanity. I would rather say certain types of insanity. Many of the inmates of asylums are suffering with congenital or post-natal organic brain

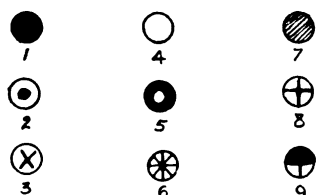
disease; these conditions are certainly not due to inheritance. General paralysis of the insane, syphilitic brain disease, and softening from vascular disease are acquired conditions and should not be classed among the inherited insanities, nor should Korsakoff's psychosis and chronic alcoholism.

FIG. 3.



This pedigree shows a marriage of first cousins. The son possessed brilliant talents, likewise a grandson, but of two other grandsons, one was insane, another a suicide. The fourth generation are all sound.

The following is the key to this figure and all the remaining figures:—



- | | |
|------------------------|-------------------------|
| 1. Insane. | 6. Brilliant. |
| 2. Physically unsound. | 7. Died young. |
| 3. Suicidal. | 8. Drunkard. |
| 4. Healthy. | 9. Drunkard and Insane. |
| 5. Nervous disease. | |

In all attempts, however, to ascertain what forms of insanity are especially due to inheritance there is always the difficulty of finding out by inquiry of the friends what was the nature of the insanity, not only because the friends do not know, but also because different opinions may be held by the medical men who have had charge of the cases, and different systems of classification and terminology have been used. Therefore, any statistical inquiry formed upon

pedigrees the data of which are based *solely* upon information which has been obtained of friends of the patient may have several radical faults. The lack of statistical evidence of heredity in relation to feeble-mindedness was noticed by Sir Francis Galton in his comments upon the Report of the Commission on the Feeble-minded, and yet the opinion of experts was unanimous in favour of the importance of heredity as a causal factor.

Two years ago an experienced biometrician and scientist, Mr. Edgar Schuster, kindly undertook to coöperate with me in the study of the convolutional pattern of the brains of relatives dying in the asylums, with a view of seeing whether, just as there is a similarity of physiognomy in the members of the same family, there is also a similarity in the convolutionary pattern. An inquiry was initiated concerning relatives at the various asylums, and a request was made that brains of relatives should be kept for examination after the necropsies had been made. Isolated instances of two or more members of the same family were known to exist by me in the various asylums; but it soon became evident that a properly coördinated card system would reveal the fact that a *very large number* of parents and offspring and brothers and sisters, besides collateral relatives, were resident in the London County Asylums, or had been recently. In June the numbers had risen from a few hundred known instances to 1834 (763 males and 1071 females), and since then, owing to a newly opened asylum not having then furnished full reports, and owing to the fact that fresh cases are continually turning up at other asylums, the numbers have now reached 2000. These instances have been afforded by the records of patients under observation during the last two years, and include their relatives who have died in, or who have been discharged from, the London County Asylums previously. A large number of cases of recurrent insanity are included in these instances—e.g., one case has a record of 23 admissions—and during the time taken for the collection of the above cases several of them have been discharged and readmitted; but at the present time it is computed that over 60 per cent. of the relative cases are still resident in the London County Asylums. But this list does not include patients with relatives in the asylums of the Metropolitan Asylums Board, nor patients with relatives in other asylums in Great Britain and Ireland.

Before proceeding to give further details of the inquiry I wish to express my indebtedness to the clerk of the asylums and the superintendents and medical officers for the valuable assistance they have afforded me in obtaining information.

STATISTICAL DATA RELATING TO INHERITANCE OF
INSANITY.

The 1834 cases are made up from 854 families as follows: 2 instances of 6 of a family, 3 instances of 5 of a family, 12 instances of 4 of a family, 85 instances of 3 of a family, and 752 instances of 2 of a family. Of the 752 instances of 2 of a family, making in all 1504 cases, it will be observed that the vast majority are directly, and not collaterally, related. Another fact stands out prominently in an analysis of the 752 instances of 2 of a family, and that is the much greater incidence of transmission from parents to offspring through the female side as the following figures show:—

<i>Parental Heredity.</i>					Males.	Females.
Father and son	44 instances	88	—
Mother	„	...	51	„	51	51
Father and daughter	58	„	58	58
Mother	„	...	104	„	—	208
<hr/>					<hr/>	<hr/>
297					197	317

It will be observed that the mother transmits to the offspring in the proportion of 60·7 per cent., the father 39·3 per cent. This is not accounted for wholly by the fact that there are more females in the asylums insane than males, for the ratio of females to males in the asylums is rather less than 11:8. Sir William Gowers in his statistics regarding insanity in the parents and epilepsy in the offspring observed that in cases with parental insanity the father was insane in 37 per cent. and the mother in 63 per cent. This, he says, is partly due to the fact that inheritance is more frequently from the mother's side by 17 per cent., and that the females are in excess by 18 per cent. It will be observed that these figures of mine closely correspond with his on the transmission of insanity from mother and father to offspring.

Cofraternal Heredity in Two of a Family.

				Males.	Females.
Two sisters	130 instances	—	260
Two brothers	87	„	174	—
Brother and sister	...	136	„	136	136
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				310	396

The above table shows when pairs of offspring of the two sexes are affected the proportion of males to females is 43·9 per cent. to 56·1 per cent., a difference of 12·2 per cent. But the percentage in which the mother transmits insanity to the offspring as compared with the father is as 60·7 per cent. to 39·3 per cent., a difference of 26·4

per cent., and this increase of 14·2 per cent. is mainly due to the fact that she transmits to the daughter nearly twice as often as the father does. It may well be asked whether this may not partly be due to the fact that the daughter, at the time of life when insanity is manifested, is more at home than the son, and therefore has more to do with her insane mother.

Grandparents' Heredity.

Female with insane grandfather	1 instance.
Male " " " "	1 "
Females with insane grandmother	6 instances.
Males " " " "	5 "

This is undoubtedly very much below the proper ratio ; it is due to the fact that there is far more difficulty of obtaining records. The hereditary transmission from females, however, markedly preponderates.

Collateral Insanity.

Female with uncle..... 12 instances	...	Male with uncle ... 11 instances
Female with aunt 33 "	...	Male with aunt ... 11 "
45 "		22 "

There is here a more marked preponderance of females affected than males than in direct heredity, but the numbers are too few to draw any very decided conclusions, except the fact that the females with aunt affected are as numerous as all the rest combined.

The proportion of collateral relatives discovered in the London County Asylums is comparatively small for several reasons: the information is not so readily obtainable, and they are less likely to come into the same asylum, as their residence is not nearly so likely to be in the same district or county as that of parent and offspring.

I have analysed the above figures, only taking into account near blood relations (parents and offspring, brothers, sisters, or brothers and sisters) where two or more representatives of the family *are now* resident in the London County Asylums. The following figures show that of an average insane population of approximately 20,000, 717 cases are thus related, representing 342 families. We may ask the question, Should we find in 20,000 adults, living in the County of London, which some random non-inheritable cause had collected together, this proportion of direct relationship? I think not.

The figures, to my mind, in a broad way, are eloquent in favour of the importance of heredity as a cause of insanity, and the numbers being great, the data indisputable facts, independent of the personal equation of the inquirer, enable satisfactory statistics to be made and

inferences to be drawn in regard to certain points relating to the hereditary aspect of mental disease.

Analysis of Instances where Two of a Family (near Blood Relations) are now Resident in the London County Asylums.

	Cases.		Cases.
Father and son	34	Two sisters	144
Father and daughter ...	58	Two brothers	80
Mother and son	44	Brother and sister ...	160
Mother and daughter ...	102		

making a total of 622 cases, representing 311 families. In addition to the above there are 95 cases in which *three* (and in two instances four) members of the same family are now insane residents in the London County Asylums—31 families. Thus the grand total is 717 cases, representing 342 families.

TENDENCY TO INHERITANCE OF DIFFERENT TYPES OF INSANITY.

When taking part in the discussion at the Royal Society of Medicine on Heredity and Disease, I expressed the opinion that, without then being able to give any precise data, the investigation I was conducting had led me to conclude that we should find among these relatives in the asylums certain types of insanity exhibit a more marked tendency to inheritance than others, and I enumerated recurrent or manic-depressive insanity, delusional insanity and the insanity of adolescence (*dementia præcox*), and imbecility as having this tendency most marked. Moreover, I observed that cases of general paralysis were relatively few in number. In the light of modern views as regards the causation of general paralysis being due to syphilitic infection, I was not surprised to find my inference was correct. Again, in the evidence which I gave before the Royal Commission on the Feeble-minded I pointed out that during the eight years ending Dec. 31st, 1902, there were 8933 patients discharged from the London County Asylums as recovered; the percentage of readmissions was 25·59, and one-half of these cases were readmitted within 12 months of their discharge. The clinical records showed that a considerable number of these readmissions were cases of recurrent insanity termed "recurrent mania" and "recurrent melancholia"; the more modern term for this periodic insanity is manic-depressive insanity. But by whatever term it is called there is one feature—viz., periodicity. When I inquired into the family histories of these cases I found insanity in other members of the family in 55 per cent., even though I did not eliminate those cases which were not visited by friends, and there was no record regarding inheritance; moreover, I found particulars of many relatives of patients being in the asylum at the time or who had previously been in there or died there. These observations

were made at Colney Hatch Asylum, where the superintendent, Dr. W. J. Seward, had for a long time been in the habit of taking the history himself from the friends who visited. I may add that this asylum has afforded valuable information in this research, partly because it is an old asylum with records often of three generations, and partly because, containing, as it does, all the Jews, one has the opportunity of comparing the incidence of inheritance of this race with the non-Jewish population. I am indebted to Dr. Seward for the following statistics relating to the percentage of relatives among the Jewish and non-Jewish population. The number of cards belonging to Jews is 80, the number belonging to non-Jewish inmates is 254. The total number of inmates is 2450, and of these 459 are Jews. So that rather less than one-fifth of the total population is Jewish. A little more than one-fourth of the relative cards belong to Jews, so that the incidence of ascertained relationship among the Jewish inmates is considerably more than among the non-Jewish. No doubt the temperament of the Jews renders them as a race more liable to the neuropathic tendency; but the greater incidence of ascertained relationship among the Jews is partly due to the following facts: They are more often visited by their friends. They have more pride of family, know more about their family, and, as a general rule, are more intelligent and anxious to afford information.

Statistics are often distrusted when an inquirer sets out to find something. I was therefore fortunate in having the coöperation of such an unbiassed statistician skilled in biometrics like Mr. Edgar Schuster. The cards were all sent to him for an independent and unbiassed investigation; his valuable report is published in the forthcoming annual report of the Asylums Committee, but I will summarise his results in great part in his own words.

There were 319 pairs of parents and children; of these the children in 69 cases suffered from periodic insanity. Of the 69 so afflicted 28, or 40·6 per cent., had parents similarly affected, while in 59·4 per cent. the nature of the parent's disease was different. Of the remaining 250 children only 41, or 16·4 per cent., had parents suffering from periodic insanity. Bratz working at Wuhlgarten Asylum, Berlin, on similar lines has obtained similar results, but as yet he has not published any statistics. He speaks of this similarity of insane inheritance as a Vererbungskreis.

There was even greater similarity of insane inheritance between brother and brother, between sister and sister, or between brother and sister, when suffering from this form of insanity, than between father and mother and son and daughter. Thus there were 200 pairs in which the first brother or sister was periodically insane, and in 92, or 46 per cent., of

these pairs the second member also suffered with manic-depressive insanity, while in the remaining 108, or 54 per cent., the two members differed in the nature of their disease.

Where the first brother and sister suffered from some other form of insanity, in only 13·8 per cent., as compared with 46 per cent., was the other member afflicted with periodic insanity, while in 86·2 per cent. were other forms associated together. This indicates similar cofraternal inheritance more than three times as frequent in recurrent insanity as in other forms. Allowing that the term "recurrent" may have been used sometimes for a second attack of mania or melancholia which was not truly a manic-depressive insanity, still it would not account for this vast difference when dealing with such a number of cases.

Delusional insanity.—Although the numbers dealt with are many fewer, yet Dr. Schuster's statistics show that the tendency of this disease to run in families is more strongly marked than between parents and offspring. The tables he gives show that delusional insanity occurs with almost four times as great a frequency (33·3 per cent. instead of 9 per cent.) than among the insane parents of other insane people, while among the brothers and sisters the frequency is just six times as great (43·2 per cent. instead of 7·2 per cent.). There is a decided tendency for the brothers and sisters of imbeciles to be also imbecile.

In dementia præcox there is a strong correlation between members of the same cofraternity. Seeing, however, that quite 80 per cent. of the cases of this form of insanity occur before the age of 25, it is not surprising to find Schuster had no available material for statistics on parents and offspring. Perhaps the term "insanity of adolescence" is a better one than "dementia præcox." The report also shows a strong correlation between brothers and sisters when affected with chronic mania or melancholia, but the numbers are perhaps too small to draw any very definite conclusions.

With regard to general paralysis he found no indication of this disease running in families. The brothers and sisters of general paralytics seem no more likely than anybody else to be themselves general paralytics, and the same may be said about their children. Of the very few cases of juvenile general paralysis recorded, only one is the son of a general paralytic.

The second problem enunciated was, Is there any tendency for members of the same family (as in some hereditary nervous diseases) to become insane at similar periods of their lives? Seeing that adolescence is the period in which stress is likely to affect the individual with an insane inheritance, it is not surprising that Schuster in his report states that "a strong tendency exists for brothers and

sisters of the same family to become insane at similar periods in their lives, and only a slight one between parents and children."

APPEARANCE OF THE BRAIN.

Since certain forms of insanity exhibit so much greater tendency to similarity of type in parents and offspring and brothers and sisters, it may be concluded that *these are the types* in which an inheritance of a tendency to insanity is three or four times as great as in other forms. Now we may ask ourselves the question, Is there any correlation between the macroscopic and microscopic appearances of brains of persons suffering from manic-depressive insanity, delusional insanity, epilepsy, and insanity of adolescence where there is no terminal dementia? It would be difficult in the vast majority of cases to discover any abnormal morphological change, nor would microscopic investigation afford much (if any) help in the elucidation of these psychoses. Indeed, I know of only one form of insanity that is really (as I have already said) an acquired organic disease—namely, general paralysis—which on macroscopic and microscopic investigation of the brain post mortem shows such change in the organ of mind as to justify a diagnosis of the form of insanity which had affected the individual during life. I do not mean to say that these psychoses may not eventuate in a dementia, and then changes may be found in the brain.

There is a disease affecting Jewish children which is quite specific in the changes observed in the brain and nervous system: I refer to so-called "amaurotic idiocy." Why it should affect only Jewish children and occasionally occur in several members of the same family is not known; nor is it explicable unless it be by an abiotrophy due to some racial hereditary condition. This disease shows a pathological change quite unlike any other disease of the nervous system that I have seen; the Nissl substance disappears from without inwards towards the nucleus, and eventually the nucleus itself dies and the whole cell undergoes a true fatty degeneration; the neurons which were the last developed are the first to go—thus the pyramidal layer of the cerebral cortex shows this fatty degeneration much more markedly than the subcortical neurons.

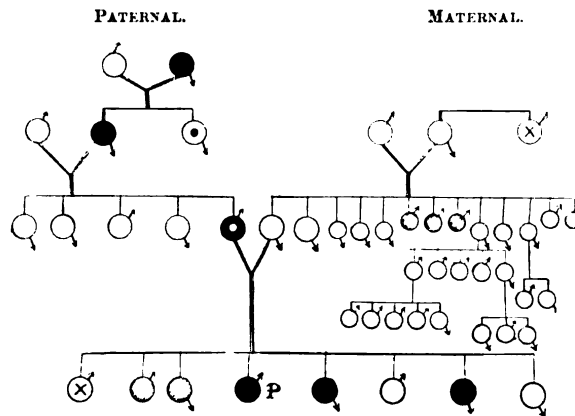
SOME PEDIGREES ILLUSTRATING INHERITANCE.

Every insane patient should be considered as a biological study. To say, merely, that one of his ancestors was insane and therefore he has a bad heredity, and to label him thus, as is the common custom, is absurd. What we wish to know is what he was born with and what has happened to him

since birth. I have found that a conversation with the mother will very much help in understanding the causes which have led up to the mental breakdown, and she is often able and generally very willing to tell all she knows about the family. I am speaking only of the poorer classes.

The causes of insanity are seldom simple; they are in varied degrees inborn tendencies combined with some form of mental or bodily stress. I use the word "stress" in its widest sense as implying a strain on the important organs and functions of the body. But it is not within the province of this lecture to deal with these causes of insanity, for my object is to dwell upon the elucidation of what were probably the inborn tendencies. The construction of a pedigree will

FIG. 4.



The patient, P, was a murderer, a brother committed suicide, and two sisters were insane; although there was a suicide on the maternal side the insane tendency came mainly from the father's stock.

often answer the question, Did the patient come from a good stock on both sides, or was there physical or mental defect or both on maternal or paternal or on both sides? The fact that a cousin was insane, or even several members of a large stock, does not show a bad heredity; often, indeed, with several insane members there will be found men of genius and men and women of great civic worth (*vide* Fig. 3). A bad stock is where we find degeneracy, insanity, drunkenness, and criminality in the pedigree (Fig. 4), or a general low standard, mental and physical, in both stem and branches of the family tree. The general tendency is for insanity not to proceed beyond three generations. As a rule, there is either a regression to the normal or the stock dies out. Not infrequently the stock dies out by the inborn tendency to insanity manifesting itself in the

form of congenital imbecility or insanity of adolescence—dementia præcox. (Fig. 5.) Such patients are especially prone to die from tuberculosis; thus "rotten twigs are continually breaking off the tree of life." (Figs. 8 and

FIG. 5.

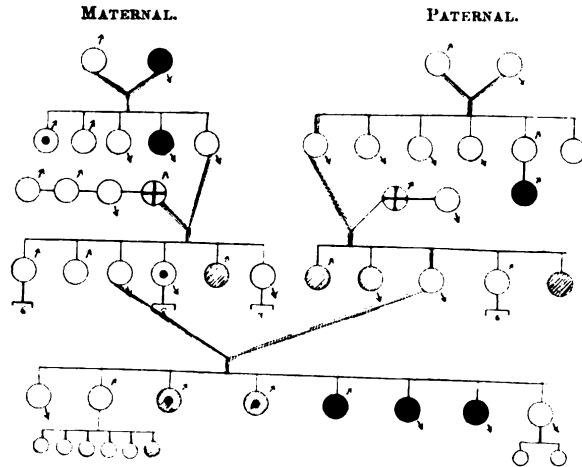
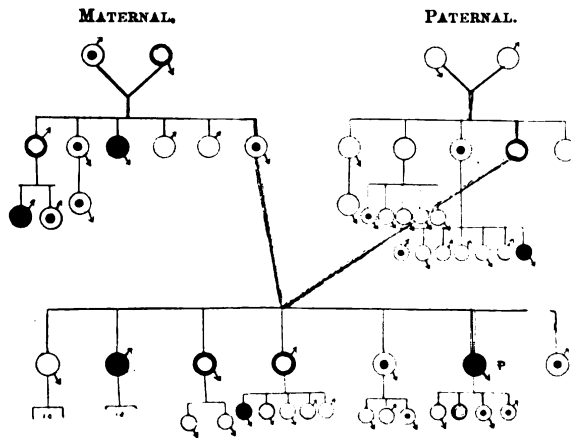


FIG. 6.



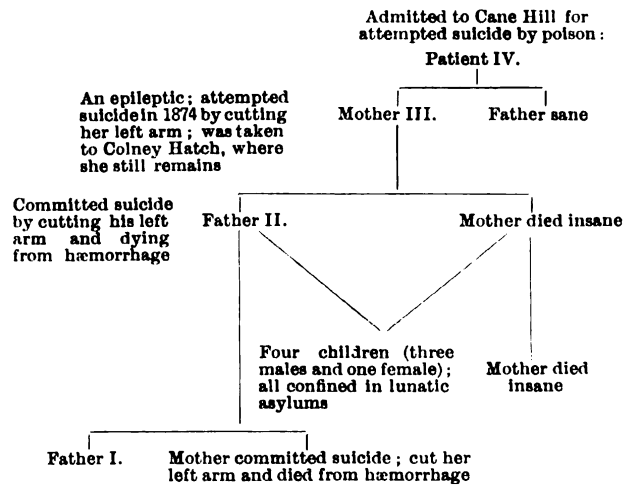
This pedigree is of a hospital patient P. suffering with neurasthenia and mental symptoms. It will be observed that nervous disease and insanity affect a number of members, especially on the maternal side.

10.) I will illustrate these facts by some examples of pedigrees.

Consanguinity does not appear to produce insanity or nervous disease provided both stocks are free from taint, but if there is insanity or epilepsy, not necessarily in the

first ascendants, but even in the collaterals, then inter-marriage of first cousins from these two stocks with collateral insanity will tend to insanity, in some cases very marked, in the offspring of the two sane related parents. I have observed in many of these pedigrees, but have not as yet compiled precise data, that manic-depressive insanity in a stock is frequently associated with suicide in the members so affected, and even in others not affected. The tendency to suicide often runs in families, and some remarkable pedigrees have been published in which members of families in successive generations have taken their lives in a particular way, and sometimes even at a particular age; there is a suicidal obsession. Morel mentions an instance where seven brothers destroyed themselves though in good position and suffering no misfortune. Mudge in the first number of the *Mendel Journal* has published a remarkable pedigree of two families that were united by marriage. In one the members committed suicide by drowning, the other by shooting. I would explain this by imitative suggestion acting on a neuropathic stock. A member of a family of four generations of suicides, of which two were inmates of the London County Asylums—namely, Colney Hatch and Cane Hill—and the pedigree of which I will now show you, affords a striking example of suicide and insanity in successive generations:—

FIG. 7.



It will be observed that in three successive generations suicide was attempted or committed by cutting the left arm.

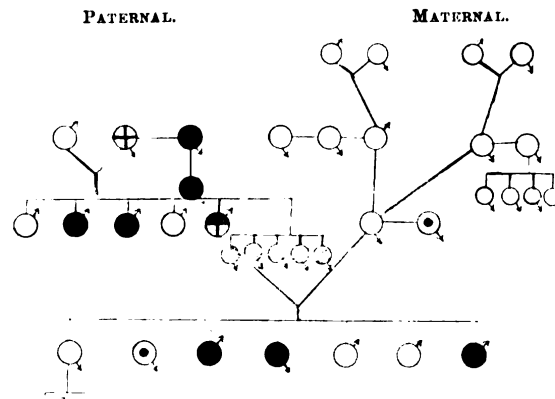
Another interesting case of a suicidal family in which a member developed impulsive obsessions of suicide and auto-mutilation occurred at Cane Hill Asylum and was published

by Dr. H. Devine, accompanied by interesting observations on the subject. The development of the obsessions in the patient dated from the aunt's suicide, which is a proof that suggestion was the cause, acting in conjunction with insane inheritance.

ALCOHOLISM.

The vexed question of transmission of acquired characters, specially in relation to alcoholism, is one of great importance and interest. That the germ cells are sequestered—"in the body and not of the body," therefore not participating in the biochemical changes which occur therein—and that in prolonged toxic conditions are uninfluenced in their nutrition and their specific vital energy, is

FIG. 8.

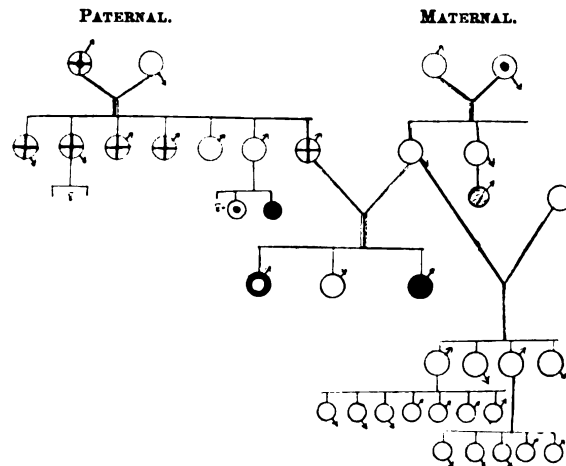


Drink and insanity in three generations; for description see text.

contrary to reason. It may therefore be asked how it is, as so often happens, a chronic alcoholic may have offspring mentally and physically sound? The question is wrapped up in the causes which lead a man to drink, and my observations seem to show that a man who can drink continually for numbers of years and keep out of a lunatic asylum, a prison, or a hospital, must have possessed an inherent stable physical and mental organisation, and he in a measure transmits this, the virility of the stock remaining potent in spite of the vicious habit, although it is undeniable that his offspring in all probability would have been stronger and better had he been a temperate man. Drunkenness in successive generations would undoubtedly lower the virility, and mental and physical degeneracy would result. Dr. Archdall Reid has expounded the tendency of the uncontrolled alcoholic type to work itself out and the same is true of other types.

I have often noticed that the children of chronic drunkards, especially when the father drank and the mother was temperate, are total abstainers. There can be no question that chronic alcoholism does figure largely in the pedigrees of patients admitted to asylums; but the same occurs—though I think not with such frequency—in the pedigrees of hospital patients. The accompanying pedigree (Fig. 8) was always regarded as a proof that alcoholism may be productive of insanity in several members of a family. The institution of the card system revealed the fact that there was collateral insanity (Fig. 8). I discovered that the sister of the drunken paternal grandmother died in Colney Hatch Asylum, where she was resident for 20 years, and her

FIG. 9.



Pedigree of a woman with two husbands. By her temperate first husband a healthy stock; by her second drunken husband only one of them sound.

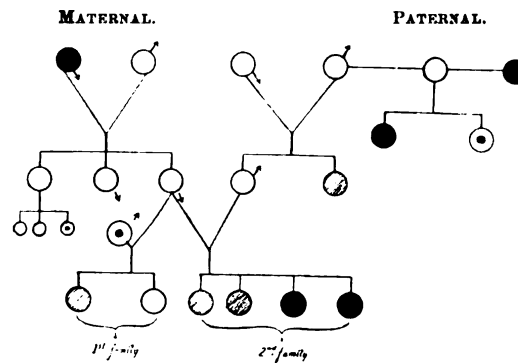
daughter, an imbecile, was at Leavesden. Further unbiased inquiries on these lines are very necessary. Occasionally I have met with a pedigree (Fig. 9), such as the one I show you, in which a woman has had two husbands; by her first husband (a temperate man) she had a family of healthy children and numerous grandchildren; by her second husband (a chronic drunkard and one of a family of drunkards of several generations) she had three children, one with a muscular dystrophy, another an epileptic imbecile, and another apparently healthy. A few cases such as this may be a mere coincidence, but multiplied, seeing that they are almost of the nature of an experiment, would form a convincing argument in support of the injurious effects of alcohol on the germ cells. It has long been the opinion that chronic drunkenness of the parents leads

to mental degeneracy in the offspring in the form of feeble-mindedness and epilepsy. With this I should agree, but that the desire for alcohol is transmitted from parent to offspring, in the form of like begetting like instead of like begetting a *tendency* to like, is without foundation. What may be transmitted is the temperament that induces alcoholism, a lack of will-power and moral sense. The transmission of an acquired character, such as the desire for alcohol, is contrary to the doctrine of heredity.

PEDIGREES OF IMBECILES, ETC.

In a number of pedigrees obtained from an imbecile asylum (Leavesden), for which I am indebted to Dr. Elkins, the

FIG. 10.



This pedigree shows the end of a degenerate stock. A woman of an insane stock marries twice; by her first husband there is one child living; by her second husband, presumably syphilitic, there are two born dead and two others in the asylum, one being a juvenile paralytic.

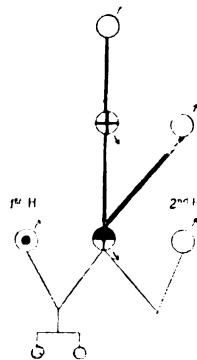
superintendent, I observe (though the numbers are not sufficient yet to give any precise data) that the families are prolific, quite as prolific as those of the pedigrees of hospital cases, but there is relatively a larger number of deaths from various diseases, especially tuberculosis. Some family pedigrees show a large number of miscarriages and stillbirths associated with imbecility and epilepsy and occasionally juvenile general paralysis. The cause of this is syphilis. (Fig. 10) The mental defect in a large number of these cases in imbecile asylums is undoubtedly due to organic brain disease and injuries at birth and after.

I have still another pedigree to show; it illustrates the transmission of a similar character and life in two generations and possibly three. (Fig. 11.) The grandfather was a

most distinguished man who lived to a great age, much respected. He had a daughter concerning whose mother no particulars were obtained. This daughter was a drunkard and of a defective moral character. She had a daughter who behaved in a somewhat similar manner, and is at present in an asylum; she has married twice. By her first husband she had two still-born children; by her second husband no children; fortunately this stock has died out.

A study of pedigrees teaches us the truth of the conclusion which Maudsley emphasises in "Pathology of Mind": "First, that a person does not inherit insanity, but a tendency or predisposition; and, secondly, that the tendency is inherited from the stock." "Nor need the unsound strain in the stock show itself in any form of actual insanity; it

FIG. 11.



Two generations of drunken mothers and the stock of a great man is ended.

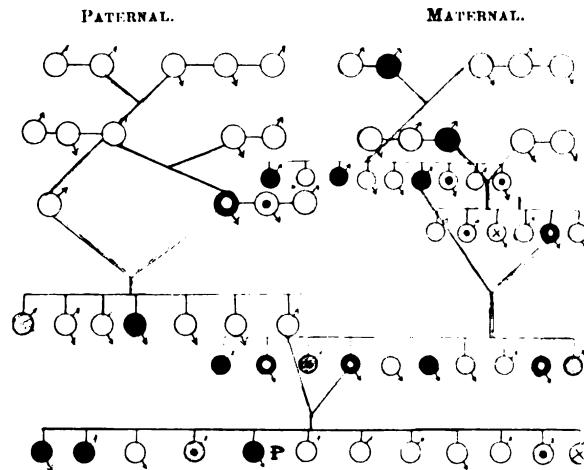
may appear in some allied nervous disorder, in hypochondriasis, in suicide, in epilepsy, in dipsomania, in weakness of mind, in neuralgias, in chorea, in stammering, in spasmodic asthma, in some periodical nerve storm of abnormal character; and conversely these disorders of one generation may in their turn forebode some form of insanity in the next generation." (Fig. 12.)

EUGENICS AND NATIONAL DEGENERACY.

With the spread of the knowledge of heredity and the interest shown among the intellectual and thinking classes by the study of such works as Whetham's "The Family and the Nation," more care will doubtless be taken in marriage selection; moreover, the cult of eugenics—literally good breeding—a term employed by Sir Francis Galton to denote the science and art of the improvement of the human race by

the double process of multiplying the fit and eliminating the unfit—is daily gaining ground. Again, the study of heredity teaches that the measure of the physical, mental, and moral capacity of the individual for civic worth and usefulness depends largely upon inborn characters; you do not gather grapes of thorns or figs of thistles. Bateson has truly said, education, sanitation, and the rest are but the giving or withholding of opportunity. The diminishing birth-rate of the

FIG. 12.



This pedigree of four generations is interesting on account of its completeness and by the large number of members of the stock on the maternal side which are affected with insanity, nervous diseases, and suicide; but there is not a single alcoholic on either the paternal or maternal side. The paternal stock is not free from taint, but the three cases of insanity and the suicide of the fourth generation, making up nearly half the living members, have for their parents a healthy father and a mother with nervous disease. It shows how necessary it is to study the maternal and paternal pedigrees in coming to any just conclusion about hereditary transmission.

professional and middle classes with the high birth-rate and diminished infant mortality of the lower classes is now agitating the minds of many, but the fact nevertheless remains that Nature cares little about individuals or societies; it is mindful only of the species, and the instinct to propagate is so rooted in our animal natures that in the process of the mental evolution of man it has become the root and stem of the tree of life upon which have been grafted the moral virtues and altruistic sentiments which are most nobly personified in maternity. We can therefore understand how the Madonna and Child has appealed symbolically to the simple faith and devotion of countless millions.

An intellectual development, whether of the individual, or community, or race, that starves the natural instincts of love, marriage, parentage, and pride of family,—these, the noblest of all human aspirations, will pay the penalty, and one way in which the penalty for the starvation of this instinct will be paid for by advanced civilisation is the increase of the neurotic, self-regarding type of temperament, the forerunner frequently of neuroses and insanity.

We are constantly reminded of the fact that insanity is on the increase; in the last 15 years the London County Council has opened four new asylums and an epileptic colony, and is now building another huge asylum; loud is the cry of national degeneracy, but when people are feeling most pessimistic about a *natural* decay of the race it would be well, if they would remember this passage from a lecture by Huxley on "Harvey and the Discovery of the Circulation of the Blood": "I myself am of opinion that the memory of the great men of a nation is one of its most precious possessions—not because we have any right to plume ourselves upon their having existed, as a matter of national vanity, but because we have a just and rational ground of expectations that the race which has brought forth such products as these may, and in good time, under fortunate circumstances, produce the like again. I am one of those people who do not believe in the *natural* decay of nations, I believe, to speak frankly, that the whole theory is a speculation invented by cowards to excuse knaves. My belief is that so far as this old English stock is concerned, it has as much sap and vitality and power as it had two centuries ago, and that with due pruning of rotten branches and due hoeing up of weeds which will grow about the roots the like products will be yielded again. The weeds to which I refer are mainly three: the first of them is dishonesty, the second is sentimentality, and the third is luxury."

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A Lecture
ON
HEREDITY AND INSANITY.

*Being the last of a Series of Six Lectures on Heredity delivered
at the Royal Institution in January and
February, 1911,*

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IN this my last lecture on Heredity I propose to deal with the subject in regard to its social and economical aspects as affecting civilised humanity. Last week I gave you some striking examples of the sudden appearance, apparently as sports, of congenital defects, abnormalities, and diseases which were transmitted through several, and in some instances through many, generations. Why, it may be asked, do these conditions not become general? Natural selection and survival of the fittest together with the constant tendency to regression to the normal average of the race is the answer. In the long procession of ages evolution has made man as he is with five toes and five fingers, and of an average stature varying from 5 to 6 ft., consequently there is always that tendency operating to maintain the normal average of the race, and the continuous operation of inheritance in the maintenance of specific racial stability is one of the biggest factors in heredity.

NATURAL SELECTION AND PREVENTION OF PERPETUATION
OF POOR TYPES.

We may now ask the question, How has nature prevented the perpetuation of poor types in man? In fact, in what way has man had to struggle for existence? All through history we shall find that as among animals and plants, so with man, the great struggle has been in the same species—viz., man with man. So the evolution of mental attributes,

intelligence, quickness of perception, courage, memory, and will power, have become gradually as essential in the struggle for existence and propagation as longevity, resistance to disease, and physical strength. It is the *brainy* rather than the *bulky* that can now survive and propagate.

The great centres of civilisation and human progress have in the past especially been built up in those regions of the earth where Nature has provided a great store of energy which can readily be utilised and converted into human energy—e.g., through ages and ages the Nile provided by its fertilising agency food for millions upon millions of human beings. But where with a lavish hand Nature provides the means for unlimited individual lives, and therefore almost unlimited propagation of the species, it enforces a constant and severe struggle for existence by which if Nature's methods are not interfered with only those possessing such mental and bodily conditions suitable for the struggle survive. In this way blood-thirstiness, craftiness, ferocity, and animal passions, combined with bodily strength and resistance to injury and disease, would in earlier times be the endowments which would best be adapted for survival.

NATURE'S MODES OF SELECTION.

However, men who gathered together in large numbers, especially when forming conquering armies, are sooner or later visited by more terrible (because unseen) foes than these human enemies. Deadly germs or habits to which either the conquering or the conquered have in the long procession of generation after generation gradually become immune, finding a new and suitable soil upon which to develop, devastate and destroy the bold and bloodthirsty as well as the cowardly and the superstitious; all alike, from the highest to the lowest, are swept away by epidemic diseases. This is well exemplified by Holbein's picture of the Dance of Death. Wars, famine, plague, spotted typhus, small-pox, syphilis, tuberculosis, malaria, and other diseases, as well as narcotics, have long been the scourges of densely populated countries. Many of the diseases are filth-begotten. Consequently those individual communities and races who have a better chance of survival in the struggle for existence are those who are most intelligent and cleanly in their habits. The recent Russo-Japanese war is the first on record in which one nation lost more men from injury than disease. This was due to the extraordinary intelligence and cleanliness of the Japanese in the conduct of their campaign, which largely contributed to their success.

During the progress of wars there is little opportunity for knowledge and learning to be displayed, yet if a nation possesses ancestral stocks endowed with inborn intellectual greatness, it is only latent during these periods of

national stress awaiting its opportunity of shining forth. This nation, impoverished by two centuries of bloody wars at home and abroad, by famine and epidemic disease, threw off the yoke of tyranny with the Reformation, and following this appeared in England an unrivalled period of intellectual development. Spenser, Milton, Shakespeare, Marlowe, Bacon, Ben Jonson, and a host of other stars of lesser magnitude blazoned forth to enlighten the world for all time. The history of the world shows that nations decay and die more often from prosperity and luxury than from striving and adversity.

MAN'S CONTROL OF NATURE IN RELATION TO NATURAL SELECTION.

Man by his discovery of the causes and prevention of disease, and his power of acquiring, accumulating, and distributing energy by harnessing the forces of Nature, has effected a control over Nature and her methods of natural selection. Hitherto Nature, unmindful of the individual and mindful only of the species in its operation of survival of the fittest, said to the blind, the halt, the lame, the diseased, the feeble of mind and body, "Thou shalt not live." In this respect Nature had no choice; her only prevention of multiplication of the unfit was to exterminate them. But civilised man, by his control of Nature's process of selection, has interfered with the laws of natural selection and survival of the fittest, and unless, as Ray Lankester says, man enters fully into the possession of his kingdom and prevents the perpetuation and multiplication of poor types, racial degeneration must follow. The proper attitude to take up in this question as regards the perpetuation of poor types, according to a well-known journalist, is that laid down by Huxley: "We are sorry for you, we will do our best for you (in so doing we elevate ourselves, since mercy blesses him that gives and him that takes), but we deny you the right to parentage. You may live, but you must not propagate."

To no class of people does this principle apply with greater force and urgency than to the mentally defective or feeble-minded. It is only within the last century that the feeble-minded have had as much chance of survival for themselves or prospect of handing down their mental and physical defects to successive generations. But all these causes which by Nature's mode of selection weed out the poor types have been controlled by man without supplying any alternative scheme of selection such as he uses with success in his breeding of domestic animals when he employs only the best types for propagating. At the present time in Great Britain restriction of families is occurring in one-half or two-thirds of the people, including nearly all the best, while children are being freely born to the feeble-minded, to

the pauper, to the thriftless casual labourers, to the criminals and others generally the denizens of one-roomed tenements of our great cities. Professor Karl Pearson keeps warning us, 25 per cent. of our population, including the above, is producing 50 per cent. of our children, and if this goes on must lead to national deterioration and degeneracy.

HEREDITY IN RELATION TO FEEBLE-MINDEDNESS AND INSANITY.

Before proceeding to the facts which I myself have collected regarding the heredity of insanity and feeble-mindedness, let me cite two remarkable instances of the evil inheritance of two separate women.

Professor Poelmann of Bonn has recorded the case of a woman, who was a confirmed drunkard and who died early in the nineteenth century, who was the direct ancestor of 834 persons. Of these 700 were known, 157 were illegitimate, 162 were professional paupers, 64 were paupers, 181 were women on the streets, 7 were condemned to death for murder, and 76 were convicted of lesser crimes.

Then there is the famous Juke's family. Ada Juke, known as the "mother of criminals," left 1200 direct descendants of whom nearly 1000 were criminals, paupers, inebriates, insane, or on the streets. The cost to the State directly in consequence of this inheritance was £260,000, while the indirect loss cannot be estimated. But these are only extraordinary and isolated instances of many.

The reading by the general public of such books as the Whethams' "Family and the Nation," the growing interest shown by the public in the work carried out by the Galton-Pearson school of eugenics, together with the publicity which controversial questions of heredity and transmission of acquired diseases have obtained, have done something to awaken the public conscience and the Government, but probably nothing has appealed more to the thinking man, and, we should hope, voter, than the rapid addition to the rates for the maintenance of lunatic paupers and feeble-minded.

Whetham remarks: "According to the mid-Victorian concept a man was either sane or insane—quite mad or completely cured. How he became mad, how completely he was cured were not taken into consideration. [I am afraid the Lunacy Laws and their application are still of that epoch.] When he was once discharged from the asylum, like the man in the old song—

'Whither he went and how he fared
Nobody knew and nobody cared.'

Such a method of treatment has had its effect in the extension of inheritance of mental inferiority. The Commissioners

estimated that the number of those persons who, while not certifiably insane, are suffering from mental defect is about 150,000, to which must be added at least another 150,000 in the asylums as well as those who have been in asylums and have been discharged."

Moreover, according to a report of Dr. Branthwaite, upwards of 62 per cent. of the persons committed to reformatories under the Inebriates Act are found to be insane or defective in varying degree; and from a study of hundreds of portraits of inebriates on the black list I am convinced that quite that proportion of such chronic alcoholics are feeble-minded degenerates frequently of a lower type than the lunatics certified and sent to asylums.

ALCOHOLISM AND INSANITY.

The general opinion, indeed, of the experts who gave evidence before the Royal Commission on the Feeble-minded was that alcoholism in one or both parents exerts its influence mainly upon the vitality of the children. It is a question, however, how far this is due to neglect, and whether the children of drunken parents, if removed from parental influence and cared for, would show a defective vitality.

The proposition which is so often made that alcohol is the principal cause of insanity should, in my opinion, be re-stated as the principal cause of admissions to asylums. There are many facts which show that the high percentage, 20-30, given by some authorities and the Commissioners in Lunacy of alcohol as the effective cause of insanity is erroneous. Alcohol in the majority of cases is only a co-efficient, and an inherited potential mental instability in these cases is the efficient cause. In support of my argument I would refer to the results of a comparison of 2000 post-mortem examinations made at Charing Cross Hospital, among which there were 110 cases of advanced cirrhosis of the liver, in the great majority of cases (60 per cent.) with dropsy, and accompanied by a history of prolonged abuse of alcohol. In my asylum experience there were relatively *very few* cases of cirrhosis of the liver and only one case so far advanced as to be accompanied by dropsy, and that was in a notorious police-court character who was convicted nearly 400 times before she was found incapable of taking care of herself. If she served no other useful purpose she was a valuable object-lesson of the inefficiency of the liquor laws. In addition to this evidence true alcoholic dementia of a permanent nature is comparatively a very infrequent condition according to my experience. Then I should like to allude to the fact that Dr. Bevan Lewis, Dr. P. W. Macdonald and Dr. W. C. Sullivan have each independently shown that there is more insanity, more pauperism, less crime and less drink in rural districts than in industrial centres and mari-

time populations, where there is more drunkenness, more crime, less pauperism, and less insanity. If we cannot convict alcoholism of being the effective cause of insanity, we certainly can of most crimes, especially of violence. Whereas drink and crime are relatively rare among Quakers and Jews, insanity is prevalent; this may be due to inter-marriage of unsound stocks. I have shown that at Colney Hatch Asylum, where there are close on 500 Jews and 2000 Christian inmates, heredity is a more important factor in the former than in the latter.

I have repeatedly observed that a quantity of alcohol which may be consumed daily by a man of inherited sound mind without apparent harm is sufficient to make a potential lunatic anti-social or certifiable. It follows, therefore, that alcohol acts as an eliminator of the unstable, the defective, and those who lack control of the animal passions. In fact, Archdall Reid in his interesting work on Heredity argues with much cogency that alcohol weeds out great numbers of individuals of a particular type, those most susceptible to its charm and to its poisonous effects upon the mind, and he reasons that alcohol, like disease, should be a cause of productive evolution. Every race, he affirms, that has had the experience of alcohol is temperate in the presence of an abundant supply in proportion to the length and severity of its past experience of the poison. This, according to Reid, is Nature's successful scheme of Temperance Reform.

Alcohol is the most effective weapon civilised man has to wipe out inferior and savage races who have previously had no experience of it.

There is no proof that the drink habit is transmitted to the offspring. I have observed that a large number of children of drunkards are total abstainers. If they take to drink it is because they inherit that weak will power and lack of moral sense whereby they, like their parent, are unable to resist the temptation to drink and acquire a vicious habit which, in spite of the misery caused to themselves and others, they are unable to resist and overcome.

TUBERCULOSIS AND INSANITY.

Another cause which in the past has been a powerful agent in the elimination of the feeble-minded and the lunatic is tuberculosis. My observations¹ on the relation of tuberculosis and insanity are based upon the collected reports of all the London County asylums with a population of nearly 20,000 lunatics extending over a period of five years. There can be no doubt that tuberculosis is especially prone to affect the insane, particularly individuals suffering from certain types of insanity—viz., imbecility, adolescent insanity, and

¹ Archives of Neurology, vol. iv.

the depressed melancholic types. Indeed, the death-rate from pulmonary tuberculosis for the insane between the ages of 15 and 35 is about 15 times that of the sane for the same age-period. It was formerly stated that the lunatics acquire the disease in the overcrowded, insanitary asylums. This is not the case; the conditions are much more sanitary than in their own homes, both as regards air-space, ventilation, and nutritious food. Moreover, it is rare indeed that a nurse or attendant of the 1800 employed suffers from consumption, and there is no proof in the few instances which have occurred that they have acquired the disease owing to their occupation. Many patients die in the asylums, having been resident there from 30 to 50 years, and show no trace of tuberculosis. This only proves that the soil as well as the seed is essential for the acquirement of this disease. Tuberculosis in the insane is due in part to an inherent nutritional deficiency, for tuberculosis and insanity affect both rich and poor. In speaking of an *inherent* nutritional deficiency I refer to a failure to assimilate food when it can be obtained in abundance. There is, however, a definite correlation between pauperism and tuberculosis and pauperism and insanity. In such case deficient supply of nutritious food is an important factor.

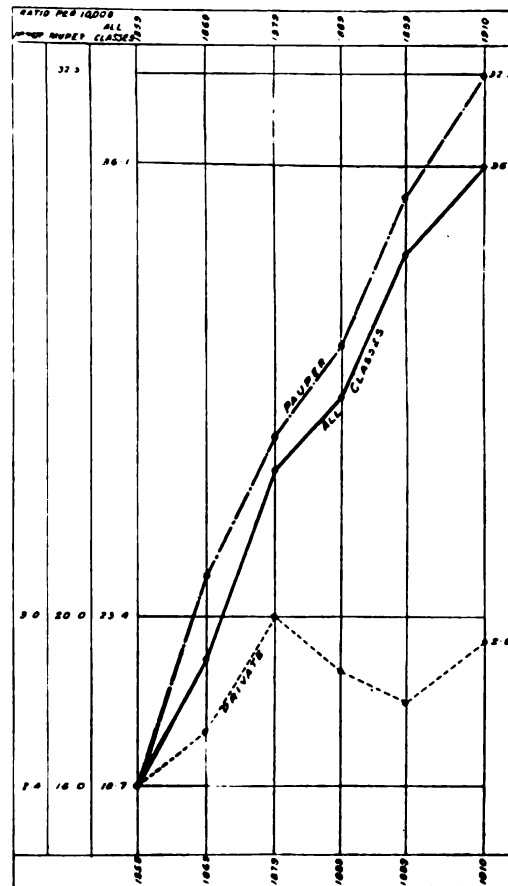
The great decline in the tuberculosis death-rate in the population which has taken place during the last 30 years is undoubtedly due to the improvement of the general social conditions of the people—i.e., the better housing of the poor, the improvements of the conditions of light and ventilation in workshop and factory, combined with cheaper food and the fall in the drink bill. Though we see this constant fall has been taking place for many years, do we see a corresponding fall in the number of lunatics and feeble-minded? Let me show you a chart (Fig. 1) indicating what has happened: it is taken from the report of the Commissioners in Lunacy. If alcohol and tuberculosis were the main causes of insanity, surely we should have had a fall, but here we have a constant rise, and this tends to prove my point—that Nature's mode of selection having been improved away by man's intelligence, he must exercise it still further by denying civic rights of propagation to certain degenerate types.

INSANITY AND SOCIETY.

What is insanity? We know so little about the minute and subtle physiological actions of the brain as an organ of the mind that we are unable to interpret the derangements and departures from the normal underlying the true insanities. We do know that all the nervous units or neurons are present at birth with all their inborn potentialities. We also know that low-grade imbeciles and idiots, as a rule, are born

with an insufficiency in numbers and a deficiency in developmental powers of the nervous units or neurons connected with the higher functions of the mind—a condition which no amount of education or feeding can rectify, because there was a failure in the germinal determinants of those nervous

FIG. 1.



Showing comparative variations in the proportion of the insane in England and Wales (and of the pauper and private classes respectively) to the total population, 1859-1910.

structures in the fertilised egg cell; for, as Thompson says, there is a general agreement among biologists that inborn variations which give every organism its individuality are the expression of changes in the intricate architecture of the germ plasma. This condition of amentia, or lack of mind, may present itself in several grades—viz., the microcephalic

idiot and sometimes the hydrocephalic idiot, in which the animal instincts are alone retained; the low-grade imbecile, who may also be an epileptic or criminal; the high-grade imbecile, who may also be an epileptic or criminal. The last-named are the most dangerous from a racial point of view because they are not segregated, and breed criminals, lunatics, drunkards, and the unemployable. I do not mean to affirm that all high-grade imbeciles are of this character. Many of those who are intellectually deficient are not morally deficient; but where by birth and nurture they are irremediably defective morally and intellectually it is useless trying to make them fit for social privileges. Again, there are those who are not intellectually deficient but who are morally defective, born criminals or perverts.

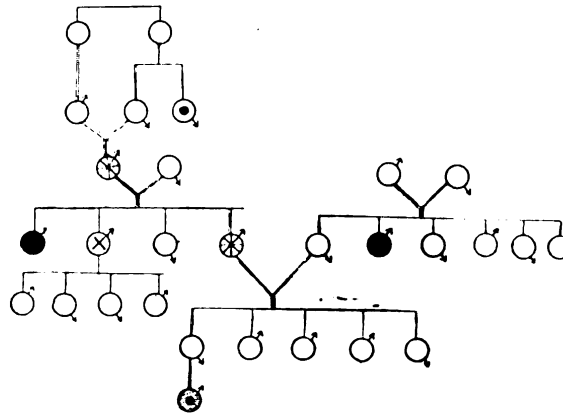
GENIUS AND INSANITY.

An individual is considered insane whose conduct is anti-social when, owing to a morbid or deranged state of his mind, he no longer thinks, feels, or acts in accordance with the usages and customs of the society to which he belongs. It is, however, hard to draw a line between eccentricity and insanity on the one hand, and insanity and crime on the other. Each are manifestations of a mental degeneracy, and may exist separately or combined. Many eccentric degenerates are insane, but are tolerated and even, in some notorious cases, adored by society, because combined with their madness there is often a streak of genius. Some of the most brilliant men in arts, science, and literature have either been insane themselves (e.g., Schumann, Lamb, Nietzsche) or have come from parents who were insane (Turner, Bacon), or there was a taint in the ancestral stocks. Men like Napoleon and Julius Cæsar were said to be epileptics; Mohamet and Martin Luther had hallucinations. Yet these men have been the foremost in making the world's history. In our times we have reason to thank a mad king for the discovery of the musical genius of Wagner, and for having made Munich the Mecca of musicians. It is true therefore that "great genius and madness are often close akin," but it is also true, as Maudsley affirms, that often the genius which is thus closely allied to insanity is of an inferior order—intense, narrow, hysterical, explosive, not calm, large, whole, and constructive. Between veritable madmen who exhibit fitful flashes of genius, madness streaked with genius, and persons with real genius who display eccentricities of thought, feeling, and conduct that speak of madness, there are a number and variety of persons who are clever but flighty, talented but unstable, intense but narrow, earnest but fanatical, all sorts of persons who, plunging into new movements good or bad and pursuing them with intemperate, perhaps distempered, zeal, lack the

just balance of the faculties, the calm equilibrium of a stable mental organisation, the true perception or mean of nature "which is the highest sanity." Maudsley further asks: "What comparison is possible between Chateaubriand and Shakespeare, between Jean Jacques Rousseau and Goethe?"

I will now throw on the screen a slide (Fig. 2) illustrating a pedigree of insanity and genius, and I may say that the genius in this case possessed in a high degree the calm equilibrium of a stable mental organisation.

FIG. 2.



Pedigree showing a marriage of first-cousins. The son possessed brilliant talents (*circle in sixths*), likewise a grandson, but of two other grandsons one was insane (*black circles*) and another a suicide (*circle with cross*). The fourth generation are all sound. *Circle with black centre*, physically unsound. The same shaded, dead.

Here is the pedigree (Fig. 3) of a great man who lived to a great age, who married beneath him, and we see the elimination of the stock. His daughter was drunken and immoral; her daughter was drunken, immoral, and insane. By her first husband she had two children born dead, by her second no children, so the stock was terminated.

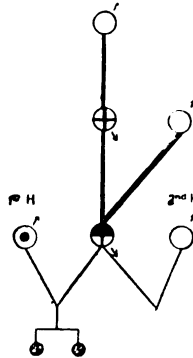
According to a recent writer on the madness of Robert Schumann it is more correct to regard the creative faculties of this musical genius and his constitutional mental disease as concomitant but independent phenomena. His genius shows itself, not in consequence of the mental malformation, but in spite of it.

Mlle. Robinovitch, in an interesting paper *La Genèse du Génie*, showed that of 74 great geniuses only ten were first-born. As a rule, the parents of great men are of ripe age when they are born; in fact, conception takes place when cellular potential is at the maximum.

HEREDITY AND SUICIDE.

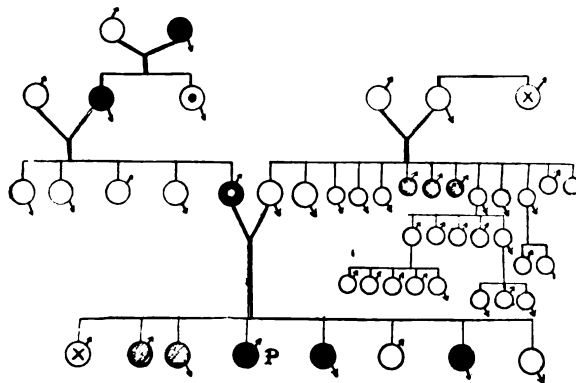
Voltaire pointed out the hereditary character of suicide, and I have met with several remarkable instances. More-

FIG. 3.



Two generations of drunken mothers, and the stock of a great man is ended. *Circle with quadrants*, alcoholism; *half black circle with quadrants*, alcoholism and insanity; *circle with black centre*, physically unsound; *small shaded circles*, miscarriage or stillbirth.

FIG. 4.

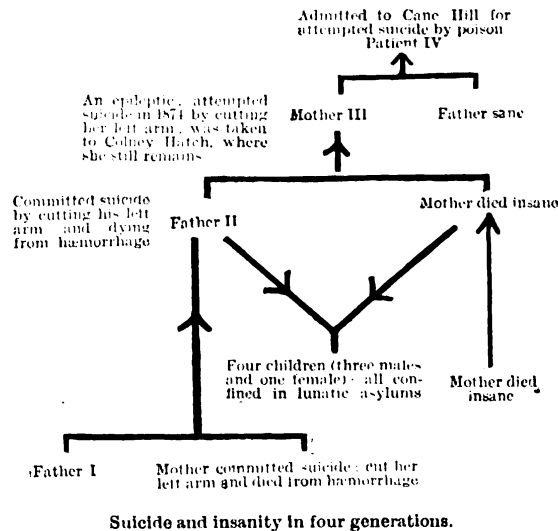


The patient (P) was a murderer (had been insane), a brother committed suicide, and two sisters were insane; all were cases of adolescent insanity. Although there was a suicide on the maternal side, the insane tendency came mainly from the father's stock. *Black circles, insanity; circle with deep black rim, nervous disease; circle with black centre, physically unsound; circle with cross, suicide; shaded circles, died young.*

over, I have observed that recurrent insanity in a stock is frequently associated with suicide in the members so affected and even in others not affected. I will throw on the screen a slide (Fig. 4) showing homicide, suicide, and insanity.

The tendency to suicide often runs in families, and some remarkable pedigrees have been published in which members of families of successive generations have taken their lives in a particular way, and sometimes even at a particular age—there is a suicidal obsession. Morel mentions an instance where seven brothers destroyed themselves though in good positions and suffering from no misfortune. Mudge, in the first number of the *Mendel Journal*, has published a remarkable pedigree of two families that were united by marriage. In one the members committed suicide by drowning and the other by shooting. Again, here is a remarkable pedigree of four generations of suicide and insanity that occurred in the London County Asylums (Fig. 5).

FIG. 5.



ZIEGLER'S THEORY OF GERMINAL DETERMINANTS.

In my last lecture I showed you a diagram which may be used to explain some of the facts of heredity, and especially in connexion with insanity and nervous diseases like epilepsy. This diagram, which I will again use (Fig. 6), serves to explain why in a tainted stock some of the offspring may escape while others are affected, and why if there is a taint on both sides the chance of tainted offspring occurring increases, while if there are intermarriages or consanguineous union not only will the offspring be more likely to be affected with the taint, but the depth of the degeneracy and the earlier age at which it will come on will be increased. This probably accounts in a measure for the prevalence of insanity among Jews and even Quakers, who are abstemious, and, as a rule, live in a clean and healthy manner.

CONSANGUINITY AND DEGENERACY.

Perhaps the most striking effects of consanguinity can be observed in some of the royal families and the Cæsars. I will throw on the screen a chart (Fig. 7) of the Cæsars,

FIG. 6.

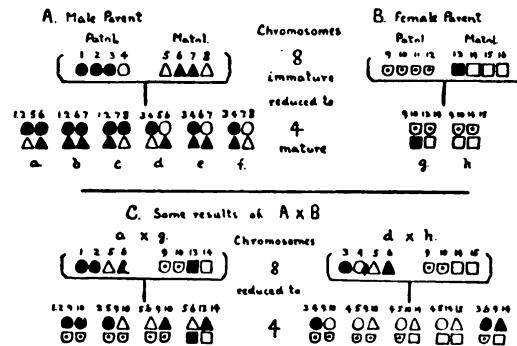
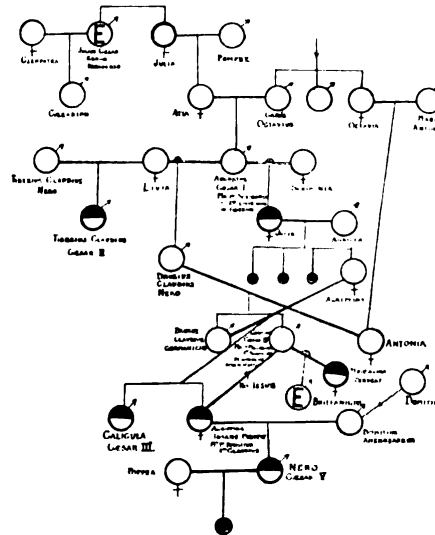


Diagram explaining transmission of a defect in different degrees by the same parents. The black figures indicate diseased germinal determinants. It will be observed that A, the male parent, inherits diseased germinal determinants from both father and mother; B, the female parent, inherits slight germinal defects from the mother. Beneath each is shown the reduction of the chromosomes (germinal determinants). In C we have illustrated some of the results of mating A and B. We can thus understand how some of the offspring are free from taint while others are markedly affected. (After E. Nettleship.)

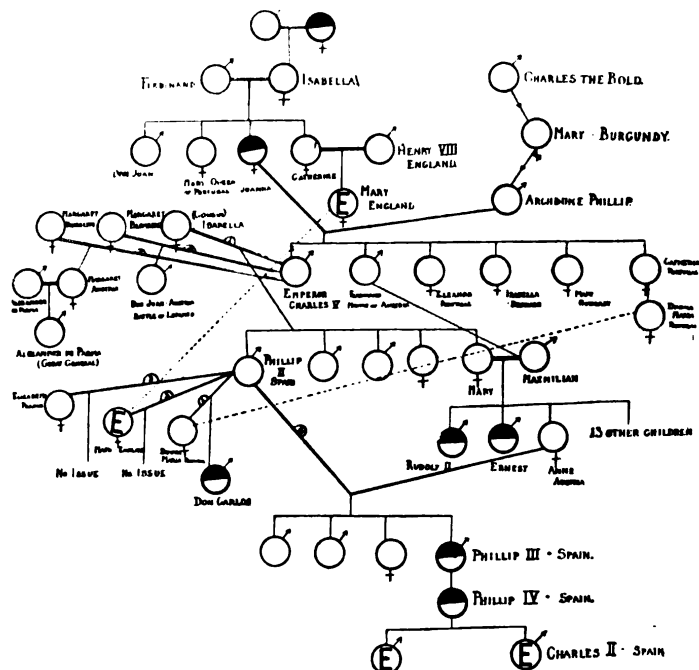
FIG. 7.



Pedigree of the Cæsars. Half black circles, insanity; circles with E, epilepsy; small shaded circles, died young.

beginning with the great Julius, an epileptic, and ending with Nero. Again, I will show you a chart of the Spanish succession (Fig. 8) illustrating an hereditary neurosis following a family for 350 years and, as Ireland says, "sometimes passing over a generation and appearing in various forms and intensities, as epilepsy, hypochondria, melancholia, mania, and imbecility, till at length it extinguished the direct royal line of Spain. The baneful tendency in the blood was, as you see, reinforced by close intermarriages with families of the same stock, and it is worthy of notice that the house of

FIG. 8.



Pedigree of Spanish Succession. Half black circles, insanity; circles with E, epilepsy.

Austria, with which the Spanish line was so often connected by marriage, had few members insane, and in the end threw off the hereditary curse. What vigour was in the first Spanish kings appeared in their illegitimate descendants, whereas those born in wedlock inherited the disease. In spite of the known ancestral taint a match with Spain was much coveted by the royal families of Europe: as an example we may recall the silly eagerness shown by James I. of England to marry his son Charles with the Infanta Maria. Whoever attends closely to history must know that there is a great deal in birth, but not birth fixed by laws and traced by heralds. 4

man who is well made, strong, mentally gifted, and able to do much work and stand much strain must be well born, and a race sodden with epilepsy, insanity, and scrofula, whatever its fictitious rank, is necessarily low born, and in reality is not worth preserving."

INVESTIGATION OF RELATIVES IN THE LONDON COUNTY ASYLUMS.

Two or three years ago I was interested in ascertaining whether there was any resemblance in the pattern of the brains of members of the same family and I sought the existence of relatives in the asylums. A few were known to me, but it soon became evident that there were among the 20,000 lunatics in the London County Asylums a very large number of near relatives and people who had been resident in the asylums or had died or had been discharged. I instituted a card system by which I was able to ascertain certain facts relating to types of insanity with which these relatives were affected and many other facts which conclusively point to *heredity* being the most important cause of insanity. There is nothing new in this—it is a generally accepted fact, but the importance lies in having ascertained that certain forms of insanity are especially liable to be transmitted either in the same form or more often in some other to the offspring. While in *acquired conditions* which cause madness and lead to people being taken to asylums—e.g., general paralysis of the insane, brain softening from arterial disease, general arterio-sclerosis, alcoholic psychosis with dementia, lead encephalitis, tumours, and senility, heredity plays comparatively little part.

A short time ago there were over 700 patients so nearly related as parents and offspring, brothers and sisters, in the London County Asylums. This of itself is a significant fact, for it is not probable that a similar number of near relatives could occur in 20,000 people brought together from the 6,000,000 of the population of London for some random non-inheritable cause. Moreover, it does not take into account relatives in other asylums or who have been discharged. The figures, to my mind, are in a broad way eloquent in favour of the importance of heredity as a cause of insanity.

LAW OF ANTICIPATION IN THE INSANE.

In the Huxley lecture which I delivered at Charing Cross Hospital last October I referred to the fact that in the pedigrees I had studied there was a general tendency for insanity not to proceed beyond three generations. As a general rule, there is a tendency to regression to the normal or the stock dies out. Not infrequently

the stock dies out by the inborn tendency manifesting itself in the form of congenital imbecility or the insanity of adolescence. Such patients, especially paupers, are prone to die from tuberculosis: thus rotten twigs are continually dropping off the tree of life. Morel in 1859 pointed out that progressive uninterrupted transmission leads finally to special degenerative forms to imbecility and idiocy, and with the diminished capability of propagation of the latter kind the stock therefore gradually becomes extinct.

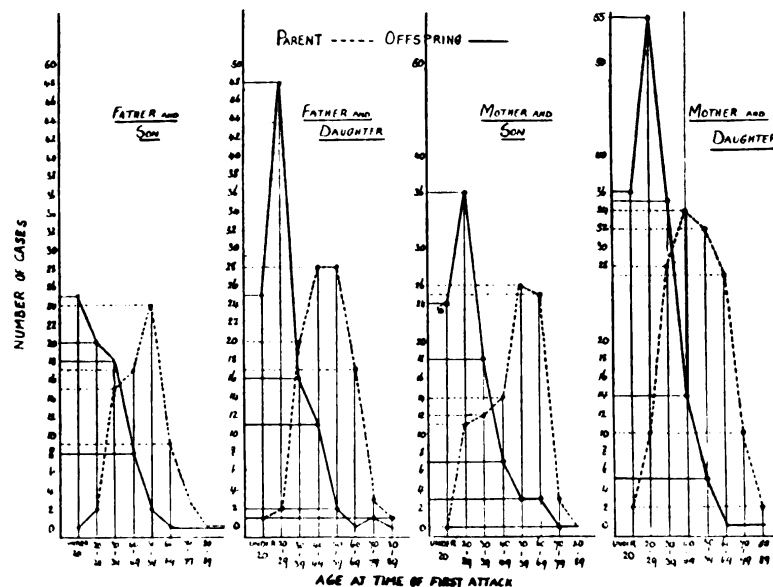
Mr. E. Nettleship observed what I had said and sent me an interesting paper² of his own on heredity. In this he points out that certain eye diseases and diabetes when transmitted occur at an earlier age in each successive generation; this fact had been observed by others and termed "anticipation"; thus owing to an interference with sexual selection or the disease killing off the patient before the age of procreation the tainted stock tends to die out, and therefore it is not often that diabetes or glaucoma, senile and pre-senile cataract, for example, are transmitted beyond three generations. Moreover, he remarks: "Anticipation or ante-dating of onset or of completion in a family disease might be taken to show the transmission of an acquired character. But it may be explained as well or better by assuming that certain defects, taints, or vices of the system, say of the blood, are not only hereditary in the true or germinal sense, but able to produce toxic agents in the embryo that have no relation to the hereditary vice, but yet may and probably do act in a similar manner as excitant of the hereditary disease."

Since then I have collected 420 pairs of parents and offspring, and the curves which I shall show on the screen illustrate the facts which this investigation shows. One broad fact illustrating this ante-dating or law of anticipation comes out, and that is that 51 per cent. of the offspring have their first attack of insanity before the age of 25; a considerable proportion of these are congenital imbeciles. This does not take into account a number of idiots and congenital imbeciles who have been sent to the asylums of the Metropolitan Asylums Board, of which I have no records. Another fact that stands out prominently and which was known since the time of Baillarger is that the mothers transmit much more frequently than the fathers to the offspring—viz., 243:177—and that daughters are affected more often than sons in the proportion of 253:167. These facts are shown in the four curves. (Fig. 9.) The base line is divided into decades, the vertical line is divided into multiples of two, and represents numbers of parents and offspring, whose ages at the time of first attack fall in the given decades. It will be observed in the first curve that

² Some Points in Relation to the Heredity of Disease, *St. Thomas's Hospital Gazette*, March, 1910.

there are 25 sons under 20; these cases are imbeciles and cases of adolescent insanity, as against one imbecile father; there are 20 under 30 against two fathers. Now when we get to the prime of life for first attack in fathers and sons the curves almost intersect at the same numbers, but whereas the sons drop rapidly the fathers rise rapidly. In the curve of the fathers and daughters it is not quite the same. There is not much difference in the curve of the fathers, but the daughters are much more numerous, and in four-fifths the age at the first attack is under 30. The curve of the mothers and sons shows that two-thirds of the sons have had their first attack under 30, whereas in the mothers

FIG. 9.



Vide text.

DATA UPON WHICH THE CURVES ARE FRAMED.

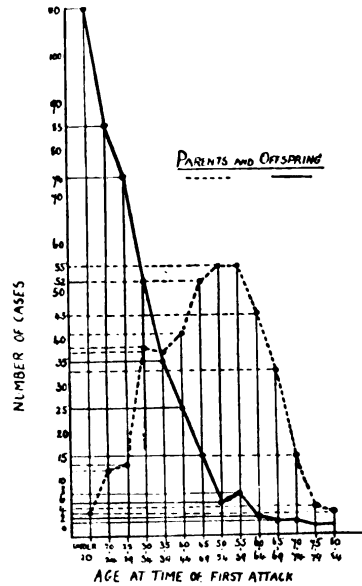
The diagrams show the relative number of cases in the combination of insane parents with insane children whose ages at the time of the first attack fall in the given age periods. Altogether 420 pairs (1 parent with 1 offspring) have been investigated.

Mother and daughter	150	pairs.
Father and daughter	103	"
Mother and son	93	"
Father and son	74	"
Total	420	"

These 420 pairs represent 774 cases and 359 families. In the case of the brothers and sisters (one brother and one sister) 152 pairs (representing 304 cases and 152 families) have been investigated.

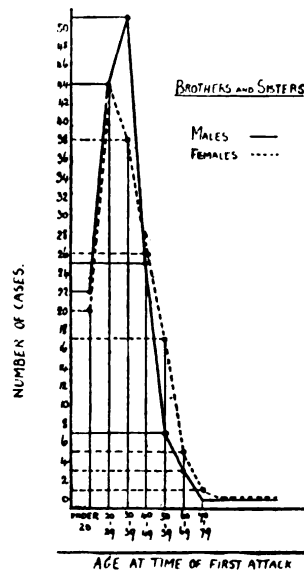
it is after 50. The next curve (Fig. 10) shows parent and offspring in one curve without separation of sexes, and exhibits the ante-dating remarkably well. The next curve (Fig. 11) shows the comparative ages at which brothers and sisters are affected.

FIG. 10.



Vide text.

FIG. 11.



Vide text.

I have investigated the age at the time of first attack in 413 instances of offspring whose mother or father has been a resident in a London County Asylum, and have found that 212 (i.e., 51 per cent.) had their first attack at or before the age of 25.

Analysis of Cards (18/2/11).—Instances of two of a family insane

	Pairs.	Cases.
Mother and daughter	111	222
„ „ son	64	128
Father and daughter	72	144
„ „ son	52	104
Brothers and sisters	163	326
Two sisters	159	318
Two brothers	106	210
Husband and wife	49	98
Other relationships, collaterals, &c. ...	138	276
Total	913	1826
108 instances of 3 of a family insane ...		324
17 „ 4 „ „		68
3 „ 5 „ „		15
1 „ 6 „ „		6
1 „ 7 „ „		7
Total		2246

Total, 2246 cases, made up from 1043 families.

These facts show that almost invariably in the case of insane parents and offspring the offspring is affected earlier than the parent, generally much earlier, on the average approximately at half the age of the parent. In over 50 per cent. of the cases the offspring were either congenital imbeciles or suffered from adolescent insanity. This law of anticipation which we see so well exemplified is of extreme importance, and I am not aware that any collection of data on a large scale has hitherto been forthcoming to show the truth of Morel's conclusions, which were based upon a large general experience combined with a remarkable insight into the nature and causes of insanity. As Ribot says, Morel's work is not sufficiently known and studied, and I owe my knowledge of its value to Dr. Henry Maudsley.

SIMILAR INHERITANCE.

Another interesting fact in connexion with heredity and insanity is a tendency of similar inheritance in certain types. I am indebted to my friend Mr. Edgar Schuster,³ who was kind enough to make a biometric investigation

³ The results of this investigation are described more fully in my Huxley lecture, *THE LANCET*, Oct. 8th, 1910, p. 1067, and the full details of the investigation are given in the Annual Report of the Asylums Committee of the London County Council, 1910.

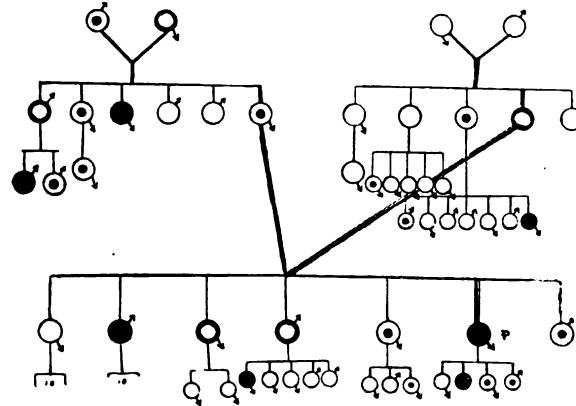
of the cards of these insane relatives for researches on this point. He found that certain types of insanity which I have always regarded as most hereditary showed a greater tendency to similar inheritance than others which I have always regarded as less hereditary or due to acquired causes. Not only was similar heredity shown in parents and offspring, but this was even more marked in brothers and sisters. The types of insanity which show similar inheritance in much greater proportions than other forms are recurrent periodic insanity, consequently persons who would be discharged as cured would tend to have offspring similarly affected. This correlation was also shown in paranoia (delusional insanity) still more markedly. Schuster noted the fact that in the case of primary dementia of adolescence there is a strong correlation between brothers and sisters or sisters and sisters and brothers and brothers, but there was no available material for parents and offspring suffering from this disease. This is not surprising when we consider the "Law of Anticipation."

THE STUDY OF INSANITY BY PEDIGREES.

Every case of insanity should be regarded as a biological problem and the study resolves itself into the acquirement of a knowledge of what an individual was born with—Nature—and what has happened after birth—Nurture. The former can only be approximately ascertained by a study of the ancestral stocks, requiring a careful inquiry and analysis of the family histories of the members in the direct line and, if possible, of collaterals. By careful attention and inquiries many important facts in respect to the transmission of a neuropathic taint can be obtained; it must always be remembered that the neuropathic tendency may be manifested in different members of the stock in different ways. Some members may suffer from some form of neurosis—e.g., chorea, epilepsy, migraine, neurasthenia, exophthalmic goitre, or diabetes. (Figs. 12 and 13.) In others it may be temperamental and manifested by eccentricity, melancholy, exaltation, feeble will-power, or lack of moral sense, manifested by evil desires or perversions. Such inherited tendencies of temperament and character may be more or less restrained by proper nurture, but given an environment in which suggestion and imitation can play their part—e.g., temptation to drink, suggestion and imitation of evil companions and surroundings, pauperism, and unemployment—and the result will sooner or later be anti-social conduct in the form of insanity, crime, or suicide.

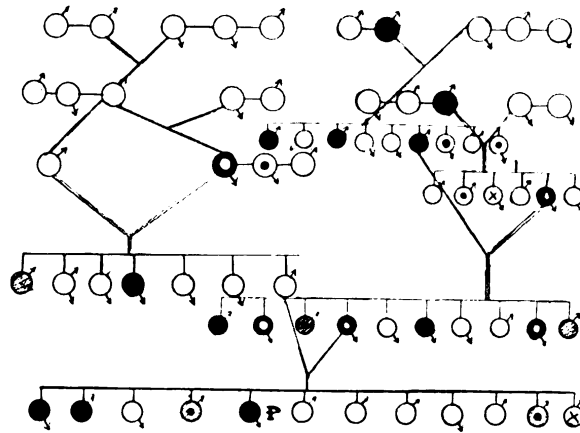
These inborn tendencies in one generation may be transmitted to the next in a more intensive form, and the product may be congenital imbecility or feeble-mindedness. I have

FIG. 12.



This pedigree is of a hospital patient, P, suffering with neurasthenia and mental symptoms. It will be observed that nervous disease and insanity affect a number of members, especially on the maternal side. *Full black circles*, insanity; *circles with deep black rim*, nervous disease; *circles with black centre*, physically unsound.

FIG. 13.



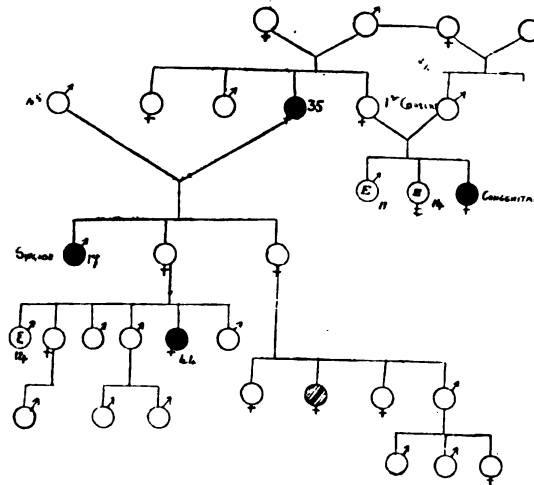
This pedigree of four generations is interesting on account of its completeness and of the large number of members of the stock on the maternal side which are affected with insanity, nervous disease, and suicide. There is not a single alcoholic on either the maternal or paternal side. The paternal stock is not free from taint, but the three cases of insanity and the suicide of the fourth generation, making up nearly half the living members, have for parents a healthy father and a mother with nervous disease. It shows how necessary it is to study the maternal and paternal pedigrees in coming to any just conclusion about hereditary transmission. *Full black circles*, insanity; *circles with deep black rim*, nervous disease; *circles with black centre*, physically unsound; *circle with cross*, suicide; *shaded*, died in early life. It was observed that the same members of the stock on the paternal side were of a melancholy temperament. The history was obtained from a very intelligent member of the family.

found this result occur from the marriage of two first-cousins who themselves were not insane, but came from a tainted stock, or in other instances, and the more numerous, there has been a union of two individuals neither of whom was epileptic or insane, but they came of two unsound stocks. According to the diagram after Ziegler (Fig. 6) we can understand why the blending of two unsound stocks should lead to a greater depth of degeneracy and an affection of a larger number of members of the stocks, but we can also see why there are chances for some members born of the union of two unsound stocks being more or less free from a hereditary taint.

Even some of the most ardent followers of Weismann and the non-transmission of acquired characters admit that environment may affect the germ plasm, and thus they would account for variations; consequently it may be assumed that alteration in the blood and lymph which nourish the germ cells may have an influence on the chromosomes or germinal determinants causing variations to arise of a pathological nature.

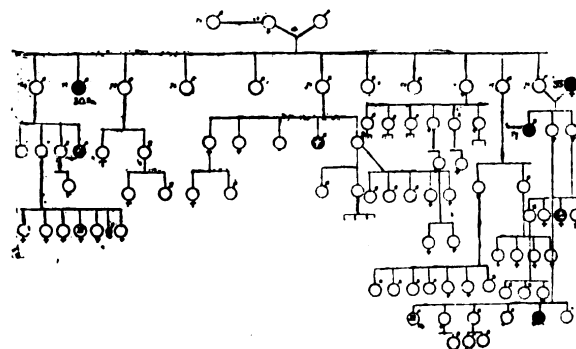
If two neuropathic stocks intermarry, or there is consanguinity in a tainted stock, the mental degeneracy is either present at birth of offspring in the form of idiocy or imbecility, often followed by epilepsy in early life, or insanity or epilepsy may occur in adolescence; and in the natural course of events this anticipation leads to the tainted stock either dying out or of elimination of its worst members, and those members who are comparatively free by breeding with a sound stock may in several generations throw off the hereditary curse. Thus Nature tends to revert to the normal. The accompanying figure illustrates the effects of consanguineous marriage of first-cousins not themselves affected but coming of a tainted stock leading to an intensification of tainted germinal determinants and all three of the offspring being affected in early life with epilepsy or imbecility; either they could not, or did not, have the opportunity of propagating, and so that tainted stock died out (Figs. 14 and 15). But, as the pedigree shows, another member, a sister who between 30 and 40 became insane, married into a sound stock, and the result was a dilution of the tainted germinal determinants; in the first generation there was a suicide; in the second, an epileptic and one climacteric insanity; several members, grandchildren, were of peculiar temperament, but in the third generation there was no trace of insanity, epilepsy, or peculiarity of temperament, thus proving the truth of Morel's opinion. The insane disposition may disappear by constantly renewing the blood by marriage with perfectly healthy families; but it is increased and developed to the most degenerate forms by further intermarriages. This was strikingly exemplified in the *Cæsars* and the Spanish Succession (*vide* Figs. 7 and 8). Morel also asserts that it may be increased and developed by drunken

FIG. 14.



Pedigree illustrating a marriage of first-cousins, who were sane, but had presumably hereditary taint. The effect of consanguinity is shown by two of the three offspring becoming affected early in life with epilepsy, and the other with imbecility, the result being termination of the stock. The pedigree also shows the effect of marrying into a healthy stock (Fig. 15), whereby the hereditary tendency in three generations has disappeared.

FIG. 15.



Pedigree of a large healthy stock, showing fertility and longevity, with mental and physical soundness of constitution. There is one instance of acute insanity which occurred as the result of an emotional shock at the age of 20, but this individual became a most prosperous man and lived to the age of 88. This pedigree also shows the connexion with Fig. 14.

fathers, &c. In respect to the last-mentioned influence, I know of no more likely cause of degenerate offspring than that produced so often in the pauper classes by the marriage or cohabitation of a drunken father with an imbecile mother. The offspring derives from the former a weak will power and lack of moral sense, from the latter a feeble intelligence, often combined with lack of will power and moral sense.

THE INCREASE OF INSANITY.

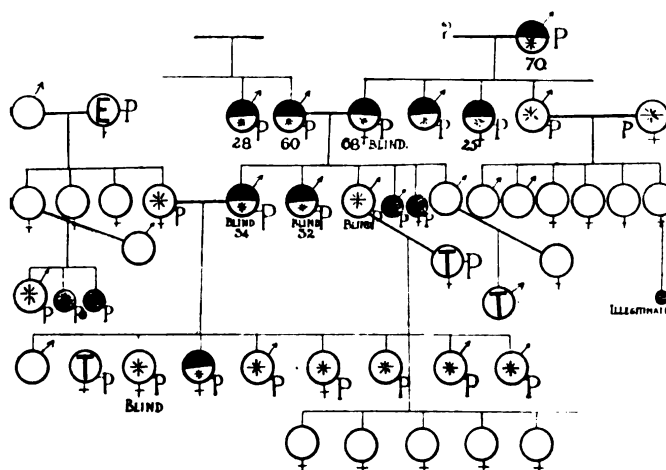
By the law of "anticipation" and by the greater liability of the feeble-minded and insane to suffer from the effects of tuberculosis, Nature is continually striving to prevent the perpetuation of poor types. But if this fact be admitted, how does it come about that insanity is *apparently* so greatly on the increase? It will be observed that I say *apparently*, for the curve shown on Fig. 1 in my opinion somewhat exaggerates the increase for the following reasons. The standard of sanity has been raised; the treatment of the insane is now most humane and quite different from what it used to be. A large number of lunatics, idiots, and imbeciles who were formerly at large are now segregated in asylums. Still, we have to remember that Nature's mode of killing off poor types has greatly diminished in activity, and numbers who formerly would have died are now taken into asylums, treated, and discharged to propagate their species. 12 per cent. of those discharged from the London County Asylums some years ago, it was found, were readmitted within 12 months. I have known one woman who was discharged and readmitted 23 times; in the meantime she had a large family. It may be that we are now reaping the harvest we have allowed to be sown by interference with Nature's mode of elimination. Again, it is probable that as fast as Nature eliminates degenerates new tainted stocks are developed by the effects of environment. Dejerine held that neurasthenia may serve as the starting-point of all the affections of the nervous system; according to him it is the source of the great neuropathological family. If it be admitted that neurasthenia be the starting-point, and this unstable nervous condition may be produced by such factors as prolonged alcoholic abuse, sexual excesses, stress of town life, with its feverish pursuit of gain and pleasure, competitive examinations, the constantly increasing departure from simple modes of life and the extension of more refined physical and mental enjoyments, bringing with them desires and emotions previously unknown, the imposition of celibacy on women and the unphysiological conditions of sexual life, whereby the maternal instinct, from which spring all the higher altruistic feelings, is starved—then it may be assumed that neurasthenia may be the reservoir which continually supplies degeneracy in its many

forms, and according to this view the cumulative effects of all these conditions in successive generations by leading to the development of the unstable neurotic self-regarding temperament of the neurasthenic forms in a stock the prelude to neurosis and insanity.

INSANITY AND PAUPERISM.

Mr. E. J. Lidbetter, relieving officer for Bethnal Green, has collected facts relating to patients who have been admitted to London County Asylums showing the correlation of insanity, pauperism, and disease. He has constructed a number of pedigrees, some of which I will now give as they are instructive (Figs. 16, 17, and 18). This work is still in

FIG. 16.

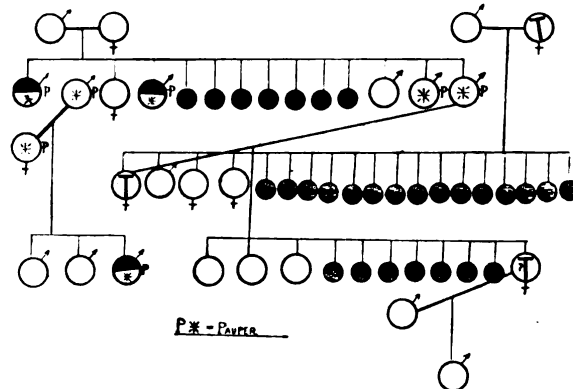


Pedigree showing transmission of insanity and blindness, and association with pauperism. *Half black circles, insanity; circle with E, epilepsy; circles with T, tuberculosis; small shaded circles, died young, &c.; circles with P and star, pauper.* The numbers denote the age at the time of first attack of insanity.

progress, and I am hopeful in obtaining the coöperation of other relieving officers when it may be possible to obtain numbers sufficient for the purpose of framing statistics. Still, some of these pedigrees confirm the opinions which I had formed that recurrent types of insanity during lucid intervals may breed a stock of potential lunatics and paupers. Again they demonstrate the fact that a high degree of fertility is frequently associated with tuberculosis and a relatively high death-rate (*vide* Figs. 17 and 18). In the Huxley lecture I alluded to similar facts which had been

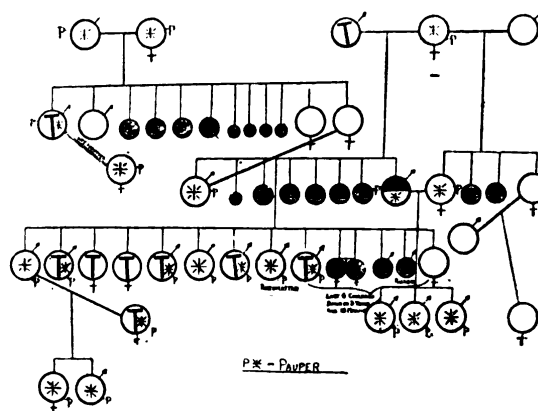
ascertained by a comparative study of the pedigrees of 40 hospital patients and 23 pedigrees kindly taken for me by Dr. F. A. Elkins, superintendent of Leavesden Asylum for

FIG. 17.



Pedigree showing association of pauperism and insanity, with marked fertility and infantile mortality. *Half black circles*, insanity; *shaded circles*, died young; *circle with T*, tuberculosis; *circles with P and star*, pauper.

FIG. 18.



Pedigree showing association of tuberculosis, pauperism, and insanity. Also shows infantile mortality and rapidity of procreation. *Half black circle*, insanity; *circles with T*, tuberculosis; *small shaded circles*, died young; *smallest shaded circles*, miscarriages, &c.; *circles with P and star*, pauper.

Imbeciles. Some interesting pedigrees also have been obtained showing that individuals are discharged from asylums, have children born in the workhouse, and later the individual is received into the asylum again, and these

children have to be maintained by the ratepayer. Fig. 19 is an example of this, as is also the following :—

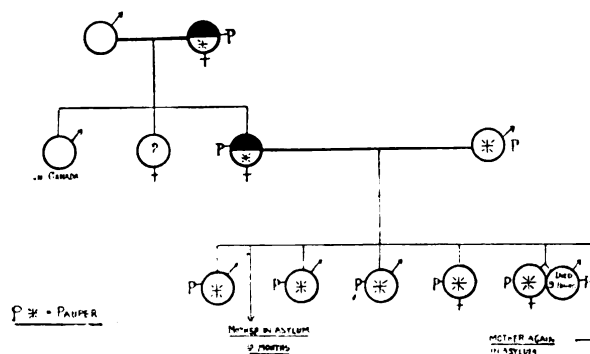
Male. First Attack at Age 15.

In asylums:—	27/1/98 to 13/8/98, Banstead.
In 1888, Bethlem and Ayrshire.	22/12/99 „ 7/4/00, „
24/12/88 to 4/5/89, Grove Hall.	7/12/01 „ 24/3/02, „
3/11/90 „ 6/2/91, Banstead.	5/10/03 „ 19/9/04, „
21/11/91 „ 2/4/92, Barming Heath.	25/1/06 „ 25/6/06, „
1/9/93 „ 18/12/93, Hanwell.	6/11/09 „ 23/5/10, „
	13/2/11 „ „

First child born 29/4/04; second child, 2/7/06; third child, 24/1/09; fourth and fifth children (twins), 24/1/10.

The whole of this family have been, on and off, chargeable upon indoor and outdoor relief since 1906, and all the children are now chargeable.

FIG. 19.



Pedigree showing association of pauperism and insanity, and the birth of offspring during the lucid interval of a case of recurrent insanity. Half black circles, insanity; circles with P and star, pauper.

CONCLUSIONS.

1. Hereditary predisposition is the most important factor in the production of insanity, imbecility, and epilepsy. It is the *tendency* to nervous and mental disease, generally speaking, which is inherited. This may be termed the neuropathic taint.

2. Education, sanitation, and the rest, as Bateson has stated, are only the giving or withholding of opportunity for good or ill.

3. Alcohol is a powerful coefficient, but not of itself the main cause, in the production of insanity, except in the rather infrequent cases of alcoholic dementia.

4. Certain types of insanity may be transmitted with greater frequency than others. This has been termed similar heredity. The types are: Periodic insanity (also termed "manic-depressive"), delusional insanity, and epilepsy. The general rule, however, is for a different type to appear.

5. Mothers transmit insanity and epilepsy with much greater frequency than do fathers, and the transmission is especially to the daughters.

6. Anticipation or antedating is the rule whereby the offspring suffers at a much earlier age than the parent; more than one-half of the insane offspring of insane parents are congenital idiots or imbeciles, or have their first attack in the period of adolescence. This adolescent insanity may take an incurable form of dementia in a large number of cases; in others it is usually mania, melancholia, or periodic insanity, and not infrequently epilepsy with or without imbecility. Very rarely does the parent become insane before the offspring. This is a strong argument of hereditary transmission, possibly hereditary transmission of an acquired character.

7. Regression to the normal average may be (1) by marriage into sound stocks, or (2) by anticipation or antedating leading to congenital or adolescent mental disease terminating the perpetuation of the unsound elements of the stock.

8. High-grade imbeciles who are not at present in any way checked in procreating owing to social conditions interfering with survival of the fittest, together with chronic drunkards, neurasthenics, and neuropaths, are continually reinforcing and providing fresh tainted stocks.

9. Recurrent insanity owing to the fact that patients are not segregated for any length of time is probably the most potent cause of insane inheritance. Facts tend to support the opinion that the recurrent types of insanity during lucid intervals may breed a stock of potential lunatics and paupers.

10. Nature is always striving to go back to the normal average and only relatively few of a stock are insane. A stock with a streak of insanity when combined with genius is not bad, and the same may be applied to a nation; but we only want a streak of genius and insanity, the great body of the nation should be of good normal average, for I believe that nation will possess the greatest potential virility in the struggle for existence that can breed from the greatest number of men and women with good bodily health who possess a large measure of the three attributes of civic worth—viz., courage, honesty, and common sense, combined with parentage, pride of family, and pride of race.

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November, 1910.]

The Comparative Neuropathology of Trypanosome and Spirochæte Infections, with a Résumé of our Knowledge of Human Trypanosomiasis.

By F. W. MOTT, M.D., F.R.S.

THE study of the diseases produced by spirochæte and trypanosome infection is primarily biological. The contagium vivum is a living organism whose activities, like that of all living organisms, are for self-preservation, and especially the preservation of the species. The chemical toxins which these organisms produce are to enable them to live and multiply. It is generally believed that the spirochætes are organisms whose characters link them to the protozoa rather than to bacteria. The *Spirochæta pallida* contracts, moves, and modifies its structure in a manner different from a bacterium. The appearance of resting forms is totally different and they arise in a different manner to the spores of bacteria. Again, the clinical aspects of affection from a spirochæte invasion differ from that of bacterial diseases and conform especially to certain trypanosome infections. There is a periodicity of the symptoms altogether unknown in bacterial diseases, but what has struck me from my own personal experience and knowledge is the great similarity of the histological lesions of the nervous tissues of chronic trypanosome infection—for example, sleeping sickness and the *mal de coit* of horses—to syphilitic and parasyphilitic lesions. Again, there is similarity in the fact that lymphocytes and plasma cells are found in the cerebrospinal fluid in trypanosome diseases of animals and man—for example, sleeping sickness. Moreover, Levaditi has shown that in point of view of sensibility in respect to hæmolysing poisons, blood corpuscles, spirochætes and protozoa generally constitute a homogeneous group, and the spirochætes correspond in this respect more to the protozoa than the

bacteria. It is probable that the periplasium of these protozoa contains a complex of lipoid substances similar to red-blood corpuscles and animal cells generally. This is an important fact, for it possibly affords an explanation of the action of organic arsenic compounds in the treatment of these diseases; for it may be that such drugs as atoxyl, soamin, "606," &c., have an elective affinity for the lecithin complex entering into the formation of the periplasium. By the periplasium I mean the osmotic membrane which covers the viscid protoplasm constituting the body of the organism. Moreover, we can understand why, when energetically pushed, they may injure the nervous system and produce neuritis by combining with the lecithin of the nervous tissue.

Trypanosomiasis corresponds with syphilis in being a disease characterized by inoculation, a period of incubation, affection of nearest lymphatic glands, followed by generalization in the lymph, then the blood-streams, and afterwards by successive eruptions, due to escape of trypanosomes from the blood-stream into the lymph spaces of the tissues, where they set up a similar tissue reaction. Moreover, in severe trypanosomiasis, as in severe syphilis, there is always, or nearly always, a polyadenitis.¹ In the central nervous system in sleeping sickness there is a chronic lymphangitis affecting the membranes and perivascular spaces, due, no doubt, to the escape of the trypanosomes from the blood-stream into the lymphatics in the same way as they escape into the vessels of the skin; they set up in the perivascular lymphatics a chronic inflammatory, endothelial and connective-tissue cell hyperplasia. Both in syphilis and sleeping sickness the location of the evidence of most severe irritation is in the region of the base of the brain; this fact may be due to a direct extension along the lymphatics of the large vessels and nerves entering the base of the skull, or to the greater amount of cerebrospinal fluid in this region and the relatively larger size of the fluid sheaths of the perforating vessels. There is one striking difference between the effects on the nervous system of infection of *Trypanosoma gambiense* and *Spirochæta pallida*, and that is that, whereas every case of this trypanosome infection leads eventually to invasion of the nervous system, in syphilis not more than 5 per cent. to 10 per cent. even of untreated cases result in invasion of the nervous system. I believe this

¹ While the *Trypanosoma gambiense* is still conveyed to man by a specific fly, the *Glossina palpalis*, it is recognized that the *Trypanosoma equiperdum* owes its power of transmitting dourine, or the *mal de coit*, from horse to horse to the fact that it has acquired the habit of perpetuating its species by multiplying in the mucous fluid found at mucous orifices. Possibly the *Spirochæta pallida* has likewise acquired new habits, and, though now transmitted direct from man to man, was at one time dependent upon a biting insect, just as now is the spirochæte of tick fever.

fact has a biological explanation. Examination of the trypanosomes with the ultra-microscope shows them to be very active, motile organisms, giving one the impression that they could readily penetrate the delicate capillary walls of the nervous system, whereas the spirochætes show a sluggish, screw-like movement. Moreover, whereas in every case of sleeping sickness trypanosomes have been found in the cerebrospinal fluid, spirochætes have never (with one doubtful exception) been demonstrated in the cerebrospinal fluid. It is probable that they only exist in the true lymphatic sheath of Robin contained in the adventitia; here they set up chronic irritation causing a localized or diffuse gummatous condition.

With this brief introduction I propose to pass on to a résumé of our knowledge of trypanosome infection as it affects the human subject in the production of sleeping sickness, and I shall conclude by a comparison of the neuro-pathology of this disease with syphilis and parasymphilis of the nervous system.

Although sleeping sickness had been described by Winterbottom as early as 1803, it was not until the beginning of the twentieth century, when the economic future of the British Protectorate of Uganda was threatened by a devastating epidemic of the disease, that the Colonial Office, inspired by Manson, approached the Royal Society with the view of appointing a commission.

Manson and I had, in 1899, investigated several cases which had come to England from the Congo, and although I have had under personal observation only a few cases of the disease, I have been from this time much interested in studying the histological changes in the nervous system. As a result of the action of Manson, a committee of the Royal Society was appointed and Castellani was sent out to Entebbe to investigate the disease. Castellani discovered the trypanosomes in the cerebrospinal fluid; but, as he had already reported a micrococcus (probably the same as the Portuguese Commission had discovered) as the cause of the disease, he did not attach to the trypanosomes the importance which they deserved; nevertheless he found them in five cases, and it is quite possible, had he continued to work at Entebbe, he would have come to a definite conclusion that the trypanosomes, and not the micrococci, were the cause of the disease.

Bruce, the discoverer of the tsetse-fly disease, was sent out, accompanied by Nabarro and Greig. They placed upon a sure foundation the causal factors of sleeping sickness: (1) By confirming and largely extending the discovery of Castellani of the existence of trypanosomes

in the cerebrospinal fluid and the blood of persons suffering from sleeping sickness; (2) by proving the existence of trypanosomes in a biting fly, the *Glossina palpalis*; (3) by correlating the geographical distribution of the disease with the geographical distribution of this biting fly; (4) by communicating the disease to animals, including monkeys, by inoculation with the cerebrospinal fluid and blood of patients suffering with the disease, or by allowing flies to bite patients having the trypanosomes in their blood, then allowing the same infected flies to feed on animals and thereby communicating the disease to the animals.

The investigations carried on by the Sleeping Sickness Commission of the Royal Society established beyond dispute that a specific organism (the *Trypanosoma gambiense*) and a specific fly (the *Glossina palpalis*), which acted as a carrier, were the essential causes of the epidemic of sleeping sickness in Uganda.

THE *TRYPANOSOMA GAMBIENSE*.

This was the name given to the organism by Dutton, and the discovery happened in this way. On May 10, 1901, Forde received under his care at the hospital, Bathurst, Gambia, a European, aged 42, the captain of a steamer on the river Gambia. The man suffered with symptoms which were regarded as malarial. Examination of the blood did not reveal malarial parasites but *worm-like bodies* concerning the nature of which Forde was undecided. A little later the patient was seen by Dutton in conjunction with Forde, and the former recognized that these *worm-like bodies* were trypanosomes. Dutton gave an excellent description of this organism, which he called *Trypanosoma gambiense*. The patient died on January 1, 1903. Dutton and Todd, in their first report of the trypanosomiasis expedition to Senegambia, 1902, described further cases of human trypanosomiasis. Of 1,000 cases examined in Gambia, six natives and one quadroon showed trypanosomes in their blood. It subsequently was shown that this trypanosome found in Gambia was identical with that found in Uganda. Dutton, Todd, and Christy, in their report upon trypanosomiasis upon the Congo, state that the organisms in the blood of individuals (whether showing signs of sleeping sickness or not) are identical, and there is no reason to suppose that the trypanosome observed on the Congo differs from the *Trypanosoma gambiense*. Moreover, the pathogenic action upon animals is the same. Thomas and Linton have made a comparative study of the human trypanosomes derived from different sources: (1) Trypanosomes brought from Gambia by Dutton and Todd;

(2) trypanosomes sent by Bruce and Nabarro from Uganda ; (3) trypanosomes of Dutton Todd, and Christy from the Congo (from the cerebro-spinal fluid of sleeping-sickness patients and from the blood of patients showing no signs of this disease). Thomas and Linton inoculated the trypanosomes from these various sources into a large number of animals, and they found that the pathogenicity was almost the same in all cases. (Nabarro). Laveran has confirmed these researches by experiments upon animals with three different strains of the human trypanosome.

Plimmer concluded from certain experiments which he made upon rats that *Trypanosoma gambiense* and *Trypanosoma ugandense* are quite distinct and separate, but Thomas and Breinl (of the Liverpool Tropical School) made experiments on a large number of rats using several strains of human trypanosomes, including the two strains used by Plimmer, and they obtained results similar to those of Thomas and Linton and Laveran. Consequently it may be affirmed that the *Trypanosoma gambiense*, originally discovered and described by Dutton, is the specific organism of sleeping sickness, whether it be acquired in the Congo State, Senegambia, Uganda, or Portuguese West Africa. In the early stages of infection the lethargy characteristic of the disease does not occur, and the case recorded by Manson, of a European lady missionary, at first exhibited only the symptoms of trypanosomiasis and was described as a typical case of infection by *Trypanosoma gambiense* ; subsequently, and for a few months prior to death, she developed the characteristic lethargy. Low and I examined the tissues of this patient and found the characteristic lesions which I had previously described. This case and many others which have died since show that the name " negro lethargy " had to be entirely abandoned, for Europeans, and in fact any human being, may be infected and die of sleeping sickness ; and there is no racial immunity against sleeping sickness. It may be mentioned that in the " Bulletin of the Sleeping Sickness Bureau " just published there is a synopsis of fifty European cases ; of these, one lived three and a quarter years and one case six years.

But the name " sleeping sickness " also should be abandoned for that of " human trypanosomiasis." There are at present in England three cases being treated for infection by *Trypanosoma gambiense* ;¹ two of these I have recently seen, and neither shows any lethargy although trypanosomes are present in the blood and the patients are subject to irregular paroxysms of fever. One case, owing to the high fever and sweating that followed, was thought (as in the original case of Forde) to

¹ I am indebted to Dr. Daniels, of the Tropical School, for his courtesy in allowing me to see these cases.

be suffering with malaria, until examination of the blood revealed the true cause. It would be better therefore to follow the convenient classification of the French Sleeping Sickness Commission. They distinguish *cas en bon état*, persons who have no symptoms whatever of trypanosome infection; *cas suspect*, persons who have symptoms which lead to further investigation; and *cas cliniques*, cases which can be diagnosed from the symptoms alone. A more accurate division, which they make when it is possible, depends on the result of lumbar puncture (Bagshawe). If invasion of the subarachnoid space has taken place, it is regarded as evidence of the patient having passed into the second or third stage; if not, he is in the first. But I shall have occasion to refer to this matter more fully later.

The evidence therefore points to the important fact that the changes found in the central nervous system—which I shall describe fully later—are due to the infection of the subarachnoid space by the parasites. It would be interesting to know if other forms of trypanosomes enter the subarachnoid space or whether it is only the *Trypanosoma gambiense*, because I have never found any lesions like those of sleeping sickness in any other form of trypanosomiasis, although sections of the brain may show swarms of trypanosomes in the blood vessels. I am inclined to think that it is the invasion of the subarachnoid space by the *Trypanosoma gambiense* which renders it so incurable. Bruce doubts whether a case is ever cured (but *vide* p. 17). The various drugs—e.g., atoxyl, soamin, mercury, trypanroth, and antimony—certainly cause the trypanosomes to disappear from the blood, but whether they will attack the organism when once it has infected the cerebrospinal fluid is the important question to be ascertained. I should doubt it, for these drugs do not pass from the blood into the cerebrospinal fluid. Seeing that the organism can easily penetrate the walls of the delicate capillaries of the central nervous system, once the subarachnoid space is invaded, there is always a reservoir for reinfection of the blood and lymph streams. Although the cerebrospinal fluid is not (owing to the absence of proteid) a suitable medium for development, yet by the production of inflammation of the meninges the fluid acquires proteid substances, and the organism obtains thereby a nutrient medium; moreover, the reaction engendered by their presence is lymphocytic, and not polymorphonuclear phagocytic.

The question arises whether the reappearance of trypanosomes in the blood may not be due to latent endocellular forms. It will be remembered that Schaudinn affirmed that trypanosomes may pass through states of endoglobular development. Since then there has been

a good deal of discussion upon the relations which exist between intracellular parasites and trypanosomes, notably concerning Leishman-Donovan bodies. Carini, in a recent paper from the laboratory of Mesnil in the Pasteur Institute, describes and figures trypanosomes undergoing endoglobular development in the blood of *Leptodactylus*. In the examination of the tissues of a large number of cases of sleeping sickness, dourine, and other trypanosome infections, I have found and described cells which presented appearances *suggesting* the possibility that there were endocellular forms; and Salvin Moore and Breinl described what seemed to be somewhat similar cell forms as occurring in the spleen, lungs, and bone marrow of rats inoculated with *Trypanosoma gambiense*; these forms they regarded as a resistant form of the trypanosome.

I will now pass on to the part played by the fly, the carrier of the disease.

THE GLOSSINA PALPALIS.

Since the publication of the Report of the Sleeping Sickness Commission in 1903, it was known that *Glossina palpalis* was the transmitter of the disease, but only recently, owing to the researches of Kleine, published in March, 1909, have we learnt that the fly after the ingestion of trypanosomes (*Trypanosoma brucei*) remains non-infective for eighteen to twenty days, but after that period it is able to infect susceptible animals. This important observation regarding the *Trypanosoma brucei* was confirmed by Bruce for the *Trypanosoma gambiense*, and the researches of Bruce and his colleagues make it highly probable that some flies may remain infective for the rest of their lives. Bruce and his colleagues made the following interesting experiment: They inoculated a monkey subcutaneously with a small droplet of fluid obtained from the gut of a fly that seventy-five days previously had been fed on an animal infected with *Trypanosoma gambiense*. The droplet of fluid prior to injection was found on examination to be swarming with trypanosomes. When the blood of the monkey was examined eight days after, trypanosomes were found, showing that it had been infected (*vide* fig. 1).

Kleine has also investigated the existence of *Trypanosoma gambiense* in the alimentary canal of flies reared from the pupa which were first fed on animals infected with that parasite, and subsequently on healthy animals. Kleine's figures exhibit a marked difference in form. The slender, red-coloured flagellates, poor in plasma, with dark nucleus he considered to be male forms. The plump, blue-stained, possessing one,

two, three, or more nuclei, he considers to be female forms. He asserts, with reason, that a sexual increase may occur even in the resting stage. Kleine, moreover, found parasites in the salivary glands, but he regards their presence as accidental, and not as playing an important part in the transmission of the disease. He found no evidence of hereditary or germinal transmissions, as Leishman has shown to occur with the spirillum of tick fever. A most important step forward has been made by these researches of Kleine, confirmed by Bruce, for we now know that some kind of development of the trypanosomes takes place in the fly after ingestion; but whether a sexual process occurs, as Kleine shows, or whether there is merely such a multiplication as occurs in cultures is not at present decided with certainty.

It was previously believed that the fly only retained its infectivity for forty-eight hours, consequently it was thought that it would be possible to stamp out the disease in an island by one day clearing out its infective population, and a few days later re-stocking it with healthy natives. Bruce remarks that it is known by experiment that the fly can retain its infectivity up to eighty days; indeed, it is probable that after a fly has become infected it will harbour the trypanosomes for the rest of its life, but what the duration of this is under natural conditions is unknown. Further experimental investigations by Bruce and his colleagues are of interest, although they by no means afford a positive solution of the question. The lake shore was cleared of the native populations in December, 1907, and had been deserted for nearly one year when the experiments began. Flies in this district were caught and allowed to feed upon monkeys, with positive results; it was therefore concluded that the *Glossina palpalis* on the uninhabited shores of Victoria Nyanza can retain its infectivity for a period of at least two years after the native population had been removed. The practical importance of this continued infectivity of the flies is undeniably great, but what the cause is, and how it can be prevented, is another matter. The experiment does not, in my judgment, prove that the flies live two years, or that there is germinal transmission. From a conversation I have had with several Europeans now in England suffering with infection of *Trypanosoma gambiense*—notably Mr. Grimes, an elephant hunter—it is impossible to control the movements of the native, and numerous means of re-infection of the flies of the district are possible; in fact, Bruce himself points out the possibility of the flies having fed on natives who frequent the lake shore in spite of prohibition; or it might be explained by the fact that the natives who were employed in

collecting the flies were the subjects of trypanosomiasis, but Bruce asserts that it cannot be by infection of the flies by natives, because precautions were taken in respect to fly-boys and canoe-men employed by the committee; or, lastly, it is possible that the mammals and birds along the lake shore have been infected, and so act as a reservoir of disease. It will be remembered that Koch thought the crocodile might be a host for the sleeping-sickness parasite.

Bruce sums up: "There remain then the two theories—long duration of life of the fly, and a local reservoir. The former at present cannot be answered, and there is no experimental proof of the



FIG. 1.

(1) Rosette form from the mid-gut ($\times 1,000$). (2-5) *Trypanosoma gambiense* from the blood of the monkey into which a tiny drop of the contents of the mid-gut of fly had been injected ($\times 1,000$). (6-13) Trypanosomes from the fore-gut of fly stained by Giemsa ($\times 1,000$).—Report 10, Sleeping Sickness Commission.

latter, since the injection of the blood of the lake-shore birds and mammals into susceptible animals has always up to the present given negative results." It appears to me that the main difficulty in accepting Bruce's conclusions is the fact that the natives may, and probably do, frequent the lake shore in spite of the prohibition.

It may certainly now be assumed that there is a period of time in which the fly does not transmit the disease after biting an infected

person; and experiments appear to show that there is a period in which it more certainly transmits the disease, and this is correlative to the finding of large numbers of trypanosomes in the alimentary tract; and, as Todd suggests, this is an indirect support of the sexual stage, which Kleine's observations so clearly indicate. Kleine found that of 410 flies which had fed on animals infected with *Trypanosoma gambiense*, 22 became infected (5 per cent.). It seems therefore necessary that both males and females should be ingested in order that the flies may become infective. Bruce was formerly of the opinion that mechanical transmission played an important part, but recent experiments published in the *Proceedings of the Royal Society*, August, 1910, led him to the conclusion that mechanical transmission plays a much smaller part (if any) in the spread of sleeping sickness than has been supposed. The researches of Bruce and his colleagues show that "cattle may act as a reservoir of the virus of sleeping sickness, and that healthy animals may be infected from them by means of *Glossina palpalis*. It has also been proved that cattle in the fly area do naturally harbour *Trypanosoma gambiense*. It is therefore possible that the cattle and antelopes living in the fly area may act as a reservoir, and so keep up the infectivity of the *Glossina palpalis* for an indefinite period."¹ The fact that the geographical distribution of sleeping sickness corresponds with that of the geographical distribution of this particular fly *a priori* is against another source of transmission, although this does not necessarily follow, for the two modes may be coincident. *Glossina morsitans*, the fly that carries the *Trypanosoma brucei*, has not as yet been shown to act as a carrier to the *Trypanosoma gambiense*.

We may next inquire what other possible means there are of the transmission of the infective organism. Seeing that a scratch in making an examination of an infected rat probably led to Lieut. Tulloch being infected with *Trypanosoma gambiense*, and his death six months later, it is conceivable that sporadic cases of infection may arise from other causes than the bite of the specific fly, and the members of the Sleeping Sickness Commission in the French Congo bring forward evidence in favour of the transmission of the disease by biting insects other than glossina; they think that mosquitoes and other biting insects are important auxiliaries conveying infection in each hut from person to person during the night. They say that in regions where the natives nurse their sick in their own houses the disease spreads with much greater rapidity than in those where they drive

¹ *Proc. Roy. Soc., B.*, 1910. lxxxii. p. 484.

them away. They give instances of one member of a family after another becoming infected, and quote instances in which a native was saved from infection, in their belief, by the use of a mosquito net. They found sleeping sickness extremely prevalent in marshy districts where *mansoniasis* abounded, and the Commission attributes to this method of infection, in some instances, the annihilation of whole villages.

Bagshawe, having thus stated the French Commission's observations, remarks that in nearly all cases there was a palpalis area near at hand or within a few miles. Moreover, why is not sleeping sickness endemic in the southern negro states of America and the West Indies, and why have there been no epidemics there? Certainly in the old slave days numbers of infected negroes must have been conveyed there. Again, the disease is endemic or epidemic only on the shores of the palpalis-haunted lakes and rivers. In Uganda, inland from the Victoria Nyanza and out of the reach of tsetse flies, no instance of infection from a sporadic case has come to light. I am informed by Dr. Grimes that sleeping sickness occurs nowhere in Rhodesia except on the borders of Lake Tanganyiki and the Loupopo River flowing from it. He also informed me that six cases of human trypanosomiasis existed at Broken Hill, and one European had died of sleeping sickness. No cases, however, had occurred in southern or north-western Rhodesia, and in those regions there is no *Glossina palpalis*.

Another possible means which had been put forward is coitus. We know that a trypanosome disease affecting equines (especially in mule-producing countries) is the *mal de coit* or dourine. In this disease a trypanosome has probably acquired the habit of direct transmission from one individual to another by multiplying in the mucous discharges of the sexual organs, and thus has arisen a new means of perpetuating the species. Koch and Kudicke put forward the hypothesis that sexual coitus explained the occurrence of the disease in women who lived in a palpalis-free area and who said they had never left it.

Kudicke's experiments support this hypothesis, likewise those of Manteuffel. The former introduced into the vagina of an uninfected monkey, taking care to avoid any injury, the blood of another monkey infected with *Trypanosoma gambiense*, and thereby infected it. The latter showed that blood containing trypanosomes placed upon a small patch of unshaven sound skin, allowed to dry and then covered with collodion, was followed in the greater number of animals by infection. These observations certainly suggest the possibility of infection by coitus. But as regards the explanation of the forty-four female patients

treated by Kudicke, Hodges offers the following suggestions: "When the epidemic first swept through the lake-shore district the men, whose employment naturally carried them into the greatest danger, usually suffered first. As the men weakened, their occupations, such as canoeing, were in part taken up by the women, who then ran greater risks and more often contracted the disease, while many of their husbands by this time had either died from it or showed obvious symptoms of its presence."

If sporadic infection does occur by one or other of the "auxiliaries" described it must be unusual; for if we are sure of one thing in the ætiology and geographical distribution of this disease in Uganda, it is coincidence with the habitat of the *Glossina palpalis*. All the facts therefore point to the conclusion that something more than mere mechanical transmission of infection is necessary—viz., an intermediate host—and we owe to Kleine's investigations the proof of this, which the following experience in Uganda practically substantiates. In the progress report of the sleeping-sickness camps in Uganda, 1909, it is stated that "hundreds of sick have for long periods been collected in places in which *Glossina palpalis* is absent, and the disease has in no case spread either to the attendants or in the neighbourhood. This has materially assisted to impress on the natives—a task at first so difficult—the truth of that which they have been taught concerning the connexion between the fly and the spread of the disease."

I have endeavoured to give a résumé of our knowledge of the ætiology of this remarkable disease—a disease not only of great interest to the medical profession, but also to the general public.

CLINICAL STUDY OF HUMAN TRYPANOSOMIASIS.

My experience clinically is limited to several negroes, including the three in which I first described in 1899 the changes in the central nervous system which accounted for the principal clinical phenomena observed during life; also of several Europeans, including the first case, whose nervous system was examined post mortem. But besides these cases of negroes which have been brought to England and the Europeans who have returned from Africa and died in England, I have had forwarded to me the material from twenty-two cases that have died in Uganda, as well as material from monkeys and other animals which have been inoculated experimentally. An account of the pathological findings in this material formed the subject of the seventh report of the Sleeping Sickness Commission.

Description of the Disease.

The following account of the clinical symptoms is based upon my own experience, the notes of the cases of which I have examined the nervous system and which died in Uganda, together with knowledge acquired by reading the admirable reports of the Portuguese Commission and French Commission, the account given by Nabarro in his valuable translation of Laveran, and Mesnil's work on trypanosomiasis, as well as a recent important progress report on the Uganda sleeping-sickness camps by Hodges:—

First Stage: Local Infection followed by Generalized Blood and Lymph Infection.—A history obtained from Europeans shows that there is a period of incubation extending from the time of infection by the bite of the fly to the time that the parasite becomes generalized in the blood. At the point of inoculation a painful red papule, which may develop into a furuncle, appears; the nearest glands may become enlarged and painful. Twelve days may pass before the constitutional symptoms manifest themselves in the form of fever and sweating. This may be accompanied by swelling of glands, but not necessarily; there is always fever, irregular, intermittent, sometimes high fever and sweating, which occur at the end of the rise of temperature. The patient usually thinks he has contracted malaria; quinine, however, affords no relief, and examination of the blood, instead of showing malarial parasites, reveals the trypanosomes. This is often associated with nervous excitation, insomnia, headache as well as prostration, weakness, and emaciation. The respiration and pulse-rates are accelerated apart from the febrile attacks. Localized oedemas, especially of the face and ankles, puffiness of the eyelids, and evanescent, congested, or erythematous patches on various parts of the body, make their appearance. These symptoms may considerably improve and even end by completely disappearing at the commencement of the second period, which marks the invasion of the subarachnoid space and the presence of trypanosomes in the cerebro-spinal fluid.

In negroes the above-mentioned symptoms are usually unobserved or even absent; consequently the diagnosis could only formerly be made by the examination of the blood. The parasites, however, are often very scanty and difficult to discover in the blood. Having been struck with the frequency of glandular enlargement, I suggested to Greig and Gray that they should examine the fresh juice of enlarged glands obtained by excision or puncture. This method for diagnosis was

performed by them, and found most useful when the organisms could not be seen in the blood. Moreover, it shows that possibly the lymphatic glands may harbour the parasites and lead to reinfection of the blood-stream and the infection of the subarachnoid space when the paravertebral glands are infected. Recent work confirms the observations of Dutton and Todd that the larger the glands the more likely are trypanosomes to be found in them. These observers, in a comprehensive investigation, have found that cervical gland enlargement without obvious cause in a native who has been exposed to the risk of infection is almost certainly due to trypanosomiasis, and should be regarded as such until the contrary is proved. Nabarro remarks: "The observations of Dutton and Todd in Gambia, and of Bruce, Nabarro and Greig in Uganda, show that in negroes this first stage is accompanied as a rule by no obvious signs of disease except the glandular enlargement above referred to." The French Commission, however, found that whereas under treatment some glands diminished in size, others did not; they concluded that the enlargement of these, though they often contained trypanosomes, was due to other causes. There are, moreover, cases in which the swelling of the glands is never very great. This was notably so in the case of a Persian who died of sleeping sickness, and whose tissues I examined. Heckenroth mentions the case of a boy who had slight suborbital œdema, and in whose blood trypanosomes were found. Not until a year later did any glands become puncturable. Heckenroth considers œdema as valuable an early sign as gland enlargement. The French Commission point out that the catamenia ceases in women and sexual desire is lost in men.

Second Stage: Sleeping Sickness, Lethargy.—The chief symptoms are fever and nervous manifestations. There is a pronounced expression of hebetude, which, once it has been seen, can immediately be recognized. The patient is indifferent to his surroundings, there is apathy and tendency to sleep or drowsiness, from which, however, he can be aroused to answer questions and for a brief period of time take an interest in what is said; but fatigue readily occurs, and, as a rule, answers are only obtained in monosyllables. He is paretic and unsteady, shuffling or oscillating in his gait. There is unsteadiness on standing, which increases on closing the eyes; there is nearly always tremor of the tongue and later of the hands when they are held out, and sometimes even when this measure is not resorted to; but there is no intention tremor. The knee-jerks are increased, and neither ankle clonus nor Babinski's sign can as a rule be obtained. The speech is slow, and sooner or later

only monosyllables are uttered ; but there is no slurring or elision of syllables, as in general paralysis, although there is some intellectual deficiency, as shown by weakness of memory, will power, and attention. Questions are comprehended as a rule, and the answers given are rational. There is no grandiose delirium, and hallucinations are but seldom noticed. There is no tendency to grandiose delusions, and the autocritical faculty is not wanting, for they keenly realize their hopeless condition. There is no optic neuritis or changes in the fundus, and the Argyll-Robertson pupil is invariably absent. The patient may remain in this condition, gradually getting more lethargic and feeble for three to six months, and then the terminal period commences in which there is profound lethargy, intense tremors and muscular weakness, loss of control over sphincters, and tendency to bed sores.

The resistance to microbial invasion is so lowered by the trypanosomiasis that the patients readily fall victims to pneumococcal and streptococcal infections resulting in bronchopneumonia and septicæmia ; it is not surprising, therefore, that pneumococcal or streptococcal meningitis complicates the clinical picture in the terminal stages of the disease, and hastens its fatal termination. In the majority of the cases of which I have examined the tissues, I have found diplococcal or streptococcal infection either of the lymphatic glands or of the central nervous system, generally both.

In the excellent clinical study published in the French report, attention is drawn to the fact that "since our arrival in the Congo the cerebral form of the disease has attracted our attention, and we have observed numerous cases of insanity and hallucinations. This acute form of the disease is known to the natives." From their observations on twenty-four whites who were patients at the Pasteur Institute, the members of the Commission conclude that there is a cerebral and medullary form. The former they divide into diffuse and circumscribed. The diffuse is manifested by mental and meningeal symptoms of a sub-acute character, accompanied by loss of the intellectual faculties. The circumscribed form is characterized by localized cortical irritation and destruction, causing epileptiform convulsions and paralysis. The medullary forms are manifested by paraplegia, with some sensory troubles and bladder affection. The cerebral forms are incurable ; the spinal progress slowly and respond to treatment. The French report also states that the mental complications of trypanosomiasis belong to the category of organic mental alienation, and are characterized before all by intellectual decadence. It may happen that the intellectual

decadence is preceded by a period of slight exaltation. Mental confusion is more or less profound, and is characterized by stupor, confusion of ideas, amnesia, and disorientation, to which may be added visual and auditory hallucinations and non-systematized delusions. The evolution of these symptoms is always rapid, in some weeks the intellectual decadence becomes very profound, and the stupor appears. These symptoms remind one rather of Korsakow's psychosis, and it may be asked whether the treatment by arsenic may not have had something to do with them. Slight optic neuritis was mentioned. Possibly owing to the patients being kept alive longer by the treatment, a deeper affection of the nervous system may have taken place. Against this, however, I may state that I found the most profound change throughout the whole central nervous system in four of the cases that died in England. The most profound changes were found in an uncomplicated case that was under Dr. Stephen Mackenzie in the London Hospital in 1890; the patient lived six months after admission, and the only symptoms noted up to a few days of death were progressive lethargy, paresis, and tremors. Three days before death he could be aroused, and could answer when spoken to in monosyllables or simple phrases, such as "Good morning"; the same occurred in the two other cases which were under my care in the Charing Cross Hospital.

Again, on looking through the notes of the twenty-one cases of which post-mortem material was forwarded to me for examination, I can find no mention of paralysis or epileptiform convulsions; in fact, the main symptoms recorded pointing to the affection of the central nervous system were progressive paresis, tremors, and lethargy. Many of them, although in an advanced stage of the disease when admitted to the hospital, were able to tell where they came from, and give an account of their previous life. Most of these cases showed an advanced meningo-encephalitis.

Hodges, whose experience is based upon 5,081 cases received at the four sleeping-sickness camps at Uganda, thus comments on the effects of modern treatment:—

"Speaking generally of the effects of treatment, it must be said that atoxyl and its allies—though possessing a marked, if transitory, trypanocidal action—have not proved to be suitable for routine administration to all classes of cases, and that no considerable number of cures can be expected to result from their administration by the methods in use. *But it cannot fail to be noticed, by those who have been familiar with the natural course of sleeping sickness before the use of modern*

remedies, that this course is, if not cut short, at any rate considerably modified by the administration of the organic compounds of arsenic."

Paralysis, paresis, and epileptiform convulsions, which among untreated cases occurred in a small percentage, are now commonly met with and are often the precursors of sudden death, which itself was very exceptional before the use of organic arsenic. Sudden or rapid death, in fact, generally preceded by cerebral symptoms, would appear now to be almost the rule among such cases as have received full courses of organic arsenic, while the prolonged lethargic stage which almost invariably marked the end of untreated cases is either scarcely noticeable or absent. It would seem probable therefore that, owing to the prolongation of the course of the disease by treatment, the nervous lesions are afforded time to become more pronounced and eventually to kill the patient, and that this may happen even though all trypanosomes may have been eliminated from the system.

If this be so, and these nervous lesions are in no way due to the treatment itself, it of course follows that, when once the disease has reached a certain stage, the lesions then existing are likely to be progressive, apart from the toxins produced by trypanosomes, and that treatment by trypanocidal drugs during or after that stage will probably be useless. When this stage actually occurs is not known, and it is doubtful whether there would be any clinical symptoms by which it could be recognized, though it has long been agreed that it is necessary to begin treatment at as early a stage as possible.

I have recently examined the tissues of the central nervous system of a case of human trypanosomiasis who was treated so energetically with atoxyl that, owing to neuritis and mental confusion and dullness, the administration of the drug could not be continued. It had been given intermittently for eighteen months, and apparently it effected a cure, for the man lived for three and a half years after treatment had been suspended, and trypanosomes, which had, early in the disease, been found in the glands and blood, could no longer be found. Death from pneumonia occurred, the man for several years having been in excellent health. I could find no evidence of the characteristic perivascular infiltration of lymphocytes and plasma cells in the brain. It is probable that the trypanosomes had never entered the subarachnoid space. A full account of the case will be published shortly in the *Proceedings of the Royal Society*. I have seen a well-marked perivascular infiltration of the subcortical tissues in a case that died nine months after infection.

Before describing fully the changes in the central nervous system in sleeping sickness, it will be advisable to consider the changes in the lymphatic glands. We shall then be in a position to compare the same with those found in the central nervous system and elsewhere.

The occurrence of irregular remittent pyrexia, in cases of infection by *Trypanosoma gambiense*, with erythematous urticarial eruptions, suggests association with paroxysmal elaboration of a poison or the multiplication of the parasite. The great frequency with which the lymphatic glands become enlarged may be associated with the paroxysms of fever and the presence of the protozoa in the glands. It has been shown that this enlargement is not due to microbial infection; it must therefore be due either to trypanosomes or a toxin engendered by them irritating the gland and causing proliferative hyperplasia of the cell elements. It is a matter of speculation whether the degenerative changes occurring in the neoplastic formation produce cytotoxins or not; probably by analogy they do not.

Histological Changes in the Lymphatic Glands.

A lymphatic gland in the first stage of swelling shows the following changes: Active proliferation of the lymphocytes in the germ-centres so that they are very densely packed together. In the lymph-cords and sinuses a very active cell-proliferation can also be observed. The oval staining nuclei of the endothelial cells lining the lymph-channels can be seen greatly increased in numbers and proliferating. Numbers of large mononuclear cells can be seen; these are round, with a deeply-stained round nucleus. They differ from the small mononuclears by the more abundant cytoplasm. Others are plasma cells of Marscholko containing a nucleus with a wheel-like arrangement of chromatin, and all stages can be traced up to the formation of a typical plasma cell and its final granular degeneration. The origin of these different types of plasma cells has always been a matter of dispute. Moreover, it is a question whether the nuclei seen in the body of branching retiform cells belong to endothelial plates, or are nuclei of branched connective-tissue cells. There is no doubt that these nuclei, when subjected to irritation, are excited to hyper-nutritive activity and proliferate, and produce mononuclear cells. There is increased vascularity of the gland, and not infrequently hæmorrhages; in fact it presents the appearance of chronic inflammation, and we must suppose that the cell proliferation is a defensive reaction to a noxious agent. The cell proliferation goes on

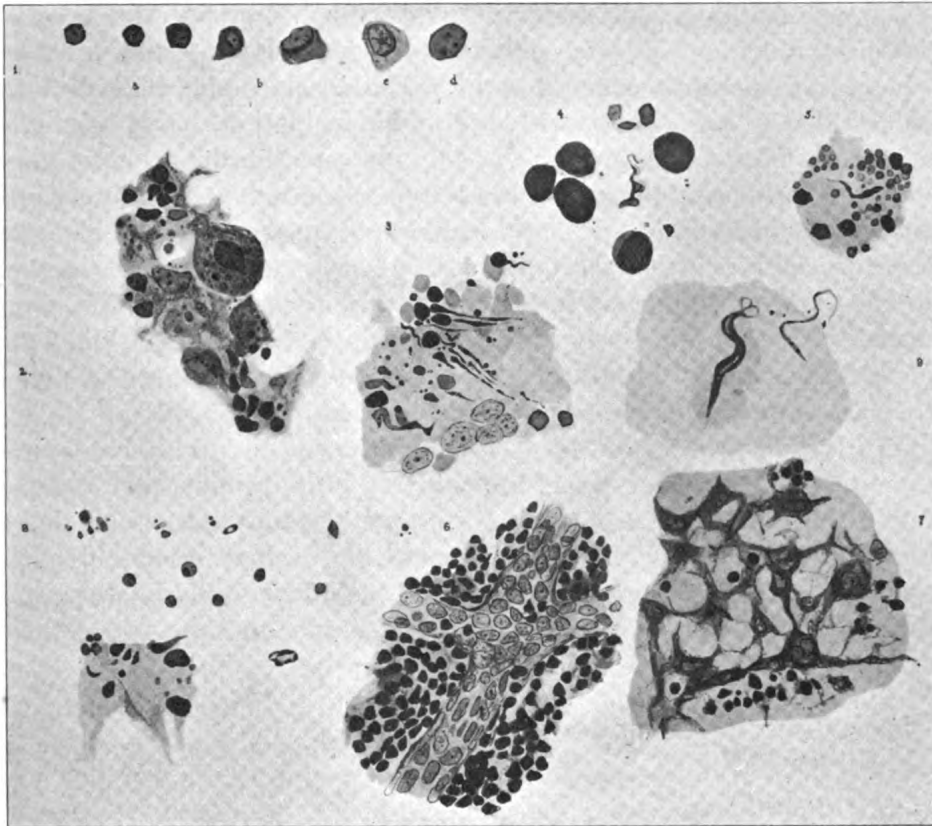


PLATE I.

CHANGES IN THE LYMPHATIC GLANDS.

- FIG. 1.—Lymphocytes in all stages of transition to plasma cells.
- FIG. 2.—Lymphocytes, plasma cells, and endothelial cells in all stages of granulo-aqueous degeneration. ($\times 375$.)
- FIG. 3.—Thread-like bodies and granules, deeply stained, seen in section of lymphatic gland. ($\times 750$.)
- FIG. 4.—Trypanosome in smear of fresh lymphatic-gland juice. Several lymphocytes and micronuclei. ($\times 750$.)
- FIG. 5.—Trypanosome in a section of lymphatic gland amidst disintegrated cell products.
- FIG. 6.—Section of lymphatic gland from a fatal case of sleeping sickness. The glands in this case were not much enlarged. There is marked proliferation of the endothelial nuclei of the lymph channel. ($\times 375$.)
- FIG. 7.—Proliferation of the connective-tissue cells of the reticulum of a lymph sinus. Marked proliferation of the nuclei of the endothelial cells seen. This change closely accords with the change observed in the perivascular lymph spaces of the central nervous system. ($\times 375$.)
- FIG. 8.—Various granules and products of cell and (trypanosome?) degeneration seen in the perivascular cell infiltration of the central nervous system. ($\times 375$.)

The preparations were stained with Leishman or Giemsa stain, and the glands used for preparation of specimens illustrated by figs. 1 to 5, inclusive, were removed during life in the first stage of the disease, before the invasion of the central nervous system had occurred.

until, automatically, an increase in numbers deprives the cells of sufficient nutrition, or they are destroyed by the virus and granulo-aqueous degenerative changes occur. These necrobiotic changes may be observed in the glands which are sterile by cultural tests for micro-organisms. In this stage there is only very occasionally evidence to be found in sections of the existence of trypanosomes. I have rarely in a very large number of sections seen any evidence of trypanosomes or their degenerated remains. Occasionally I have found the dead parasite in the form of attenuated thread-like forms, or macronuclei or micronuclei. According to Greig they can always be discovered in the fresh juice of the enlarged glands, but Thomas and Anton Breinl consider that they are not more numerous in the glands than in the blood.

In the third stage of very chronic cases, a few of which I have examined (one removed during life and sterile), the products of degeneration had been in great part absorbed, and the gland had become dense and fibrous. This is the final sclerous change that occurs in other chronic neoplastic formations, the fibrous conjunctival elements preponderating over the cellular elements. As a rule, in sleeping-sickness cases, death occurs before this can take place.

Morbid Changes in Lymphatic Structures.

All the observers from the earliest times have noticed the enlargement of the lymphatic glands; and Greig, at my suggestion, punctured the glands and examined the fresh juice. He is of opinion from his observations that this is an easier and more reliable mode of determining the existence of *Trypanosoma gambiense* than examination of the blood or cerebrospinal fluid. Dutton and Todd came to the same conclusion working in the Congo State. Many natives in Uganda and the Congo State have, however, enlarged glands, and yet are not the subjects of sleeping sickness. They may be, however, and probably in nearly all cases are, candidates for the disease.

Do the trypanosomes get into the glands and multiply there, setting up a chronic inflammatory process which terminates in fibrosis? The glands may be inflamed and enlarged and yet be sterile as regards micro-organisms. It is probable that trypanosomes infect the lymphatic glands by escaping from the ruptured capillaries, or they may have become infected by the cerebrospinal fluid when this secretion contains trypanosomes. Similarly by capillary hæmorrhage the trypanosomes may infect the cerebrospinal fluid and the lymphatic structures of the

central nervous system. If the trypanosomes can set up chronic inflammatory changes in the lymphatic glands (as there is no doubt they do), and microscopic examination of sections reveals but occasional and scanty evidence of their presence, it is quite reasonable to suppose that they can similarly produce chronic inflammatory changes in the lymphatic structures of the central nervous system. We do not know if the trypanosomes produce this chronic irritation by their mere mechanical presence, which seems unlikely, seeing that vessels may be crammed with trypanosomes in nagana and surra without causing lymphangitis. There is, according to Plimmer, Thomas, and Anton Breinl, however, no experimental evidence that trypanosomes produce a chemical toxin; although that would seem the most probable cause of the chronic inflammatory change. The numbers of trypanosomes found in the cerebrospinal fluid are in no way proportional to the changes found in the central nervous system. Yet there is considerable evidence (*vide* Sleeping Sickness Reports, Royal Society) to show that not until trypanosomes are found in the cerebrospinal fluid does the chronic inflammatory change take place. If they existed in abundance instead of sparsely, we might consider that this fluid afforded a suitable medium for their propagation, and the absence, normally, of lymphocytes in this fluid might be counted a cause. On the other hand, the small quantity of proteids which the cerebrospinal fluid contains would not admit of suitable nutrition.

The posterior spinal ganglia always show some chronic changes, proliferation of the endothelium of the lymphatic capsules of the ganglion cells, together with interstitial lymphocyte accumulation, and these chronic changes may be due to the absorption of toxins from the neighbouring infected paravertebral glands.

In practically all cases of sleeping sickness the cervical glands are enlarged, and the most chronic change is found about the base of the brain. Hence a possibility that the chronic inflammation of the lymphatics spreads along the nerves, spinal ganglia and roots to the central nervous system, and especially along the lymphatics of the nerves and vessels entering the base of the skull. Examination of other tissues—e.g., the heart, pericardium, liver, alimentary canal, and testicles—shows, though generally speaking in far less degree, an infiltration and accumulation of lymphocytes in the lymphatics, suggesting a chronic inflammatory reaction of the lymphatics.

The Histological Changes in the Central Nervous System.

Observations of Bruce and his colleagues show that it is the invasion of the subarachnoid space by the organisms which cause this change, and my observations and experience show that there is a parallelism between the depth of the lethargy and the diffuseness and intensity of the lymphatic perivascular infiltration.

In the seventh report of the Sleeping Sickness Commission of the Royal Society I stated, as the result of an examination of a large number of sections stained by polychrome and eosin, Mallory and Heidenhain-eosin methods, that the meningeal-cell infiltration was the result of an irritative process affecting the pia-arachnoid serous membrane, which was manifested not only by a proliferation of the neuroglia cells but also by a proliferation of the endothelial-cell nuclei and an infiltration of the pia-arachnoid membrane with lymphocytes, which may become transformed into plasma cells. But sections do not show the mode of origin of these cells in such a clear and demonstrative manner as the following methods which I adopted. The pia-arachnoid membrane was stripped off small portions of brain from a number of cases of chronic sleeping sickness, including the European case under Dr. Bradford, which was of unusual value, because there was no terminal or secondary microbial infection, and because there was *no noticeable enlargement of the lymphatic glands*. Small portions of the stripped-off membrane were divided by tearing rather than cutting, so that the thin frayed edges could be examined under a high power of the microscope. They were stained by hæmotoxylin and eosin, Leishman's stain, polychrome and eosin, and Eisath's modified Mallory stain, and mounted in Canada balsam. Several interesting facts were observed. *The fibres forming the interlacing network were coarser than natural and much increased*. Many of the vessels were gorged with blood and there were *many capillary hæmorrhages*. A variable number in different cases of large cells containing blood-corpuscles or altered blood-corpuscles were seen, similar to those seen in sections. These cells were usually oval, sometimes round, with the oval or round nucleus pushed up to one end. Sometimes the cytoplasm contained discrete corpuscles, sometimes this *endothelial macrophage* had digested the corpuscles and the cytoplasm had assumed in consequence a uniform orange stain. Some of these cells containing blood-pigment had undergone nuclear proliferation; four or five deeply-stained, round nuclei could be seen in one cell. The adventitial sheath of the arteries can be

distinctly seen, and there is often evidence of endothelial-cell proliferation shown by an increase in the number of large, pale oval nuclei, many of which could be seen undergoing mitosis and proliferation; they resembled the endothelial nuclei seen in the lymph sinus of the lymphatic glands, but the great mass of cell infiltration is in the meshwork of the pial trabeculæ of the subarachnoid space and its prolongation as a sleeve around the vessels entering the grey matter.

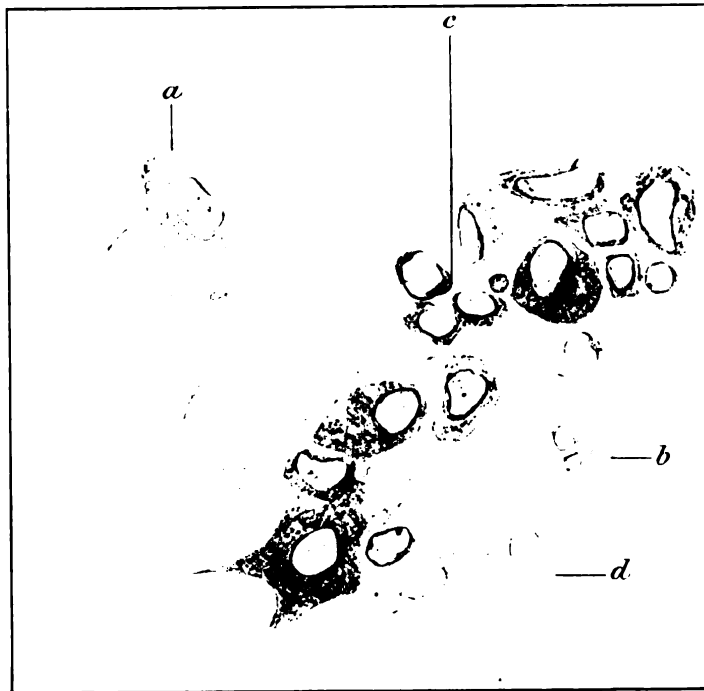


FIG. 2.

Small portion of pial-arachnoid tissue stained by Eisath's modified Mallory method mounted on the flat. ($\times 500$.)

Preparations stained by logwood and eosin and Van Gieson's fluid exhibit two kinds of nuclei—viz., (1) large, pale, oval, less often roundish nuclei, with a delicate nuclear membrane and very fine intranuclear network, similar in all respects to the oval nuclei of a lymph sinus; (2) smaller round or irregularly shaped more deeply-stained nuclei with a narrow investing cytoplasm, also large cells containing similar deeply-stained nuclei, and not infrequently some cells, two or more, even as many as six, round nuclei, which are sometimes unequal in size

and always uniformly, diffusely, and deep stained throughout. These cells are endothelial cells undergoing endogenous nuclear proliferation.

The endothelial cells of the lymphatic sheath of Robin and the endothelial plates lying upon the trabeculæ of the subarachnoid space and the pial sleeve of the vessels, as the result of the chronic irritation produced by the presence of the trypanosomes in the cerebrospinal fluid, undergo a progressive formative hyperplasia similar to that of the lymphatic glands.

In preparations stained by Eisath's modified Mallory stain, I have observed large flat endothelial cells without any processes exhibiting the following appearances of hyperplasia: (a) With the cytoplasm stained pink, and with an oval or round nucleus in the centre stained light yellow; (b) the same form of cell can be seen undergoing endogenous nuclear proliferation; (c) the same form of cell dividing or divided into small mononuclears in which there is only a relatively small surrounding pink-stained cytoplasm. Besides, we find cells which morphologically resemble the branched retiform cells of connective tissue of the lymphatic gland, with a large oval unstained nucleus. These nuclei appear to undergo division to form hyaline mononuclear cells which are seen proliferating in the inflamed lymphatic glands. The increase of the large and small mononuclear lymphocytes in the blood may be due to this cell hyperplasia in lymphatic structures. The meningeal and perivascular infiltration is due not only to active endothelial-cell proliferation *in situ*, but also to accumulation of the lymphocytes by conjunctival proliferation and consequent obstruction to the outflow of the lymph along the vessels, also obstruction to the escape of the cerebrospinal fluid from the cranio-spinal cavity. The infiltration is found especially around the vessels having a lymphatic and pial sheath; this sheath disappears on the smallest vessels, therefore we can easily understand why it is that the smallest vessels and capillaries show little or no investing sheath of cell infiltration. However, in chronic cases, lymphocytes, and especially plasma cells, can be seen closely applied to them. Do the branching processes of the *neuroglia cells* form a meshwork around the larger vessels and cause obstruction, or is the meshwork in which the mononuclear cells lie merely the thickened and proliferated trabeculæ of the connective-tissue cells of the lymphatic and pial sheath? My answer is that the infiltration around the large vessels and in the membranes entirely corresponds in appearance with the infiltration which I have described in patches around the vessels of the visceral layer of the

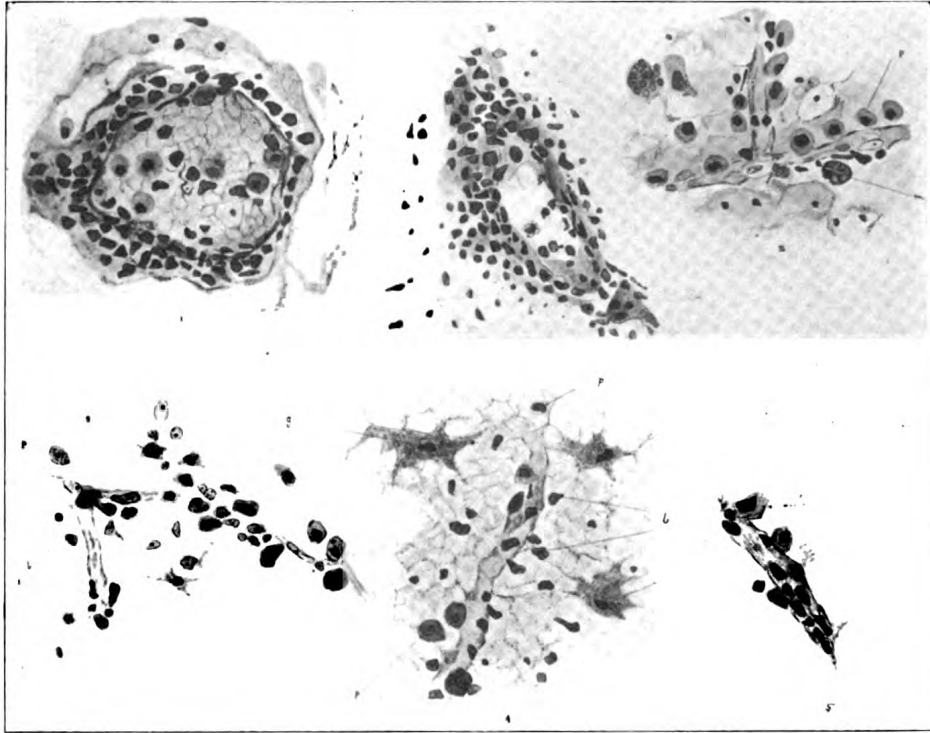


PLATE II.

CHANGES IN THE PERIVASCULAR LYMPHATICS OF THE CENTRAL NERVOUS SYSTEM, &c.

- FIG. 1.—Transverse section of a small vessel of the medulla oblongata, showing perivascular infiltration with lymphocytes. Many of these have a hyaline appearance. The lumen of the vessel contains blood corpuscles, large and small mononuclear leucocytes, and a trypanosome is seen in the centre. This was the appearance presented by the vessels throughout the cortical and subcortical structures. The preparation was obtained from a very chronic case. ($\times 375$.)
- FIG. 2.—Small vessel with plasma cells (*p*) and morular cells (*m*). ($\times 375$.)
- FIG. 3.—Small vessel dividing into two capillaries, showing nuclear proliferation of the endothelial cells. In the neighbourhood are plasma cells (*p*), lymphocytes (*l*), and glia cells (*g*). ($\times 375$.)
- FIG. 4.—Three large neuroglia cells (*g*), their branches ending in a network around and upon a small vessel. In the meshes are lymphocytes (*l*) and plasma cells (*p*). ($\times 375$.)
- FIG. 5.—Small vessel with proliferation of endothelial nuclei and two plasma cells (*p*).
- FIG. 6.—A transverse section of a vessel in a very chronic case of sleeping sickness in a European, showing marked perivascular infiltration with lymphocytes. ($\times 187.5$.)

pericardium in the lymphatic spaces of the heart muscle and the perivascular lymphatics of the liver and the testis. Moreover, *I am unable to trace the processes of the neuroglia cells any farther than the outer sheath of the infiltration.* Again, no place shows the perivascular and meningeal infiltration better than the lymphatic and pial sheaths of the vessels in the soft membranes covering the cerebellum and their extensions between the folia, *yet there are no neuroglia cells seen in the adjacent cortex of the cerebellum,* although the neuroglia cells are seen in abundance in the white matter. The neuroglia proliferation is therefore not essential for the production of this characteristic perivascular cell infiltration. As a rule, the subcortical perivascular infiltrations are more marked and extensively diffused than the cortical, and this is especially evident about the base of the brain and around the perforating arteries; this corresponds in a way with syphilitic brain disease. Sometimes when there is but little evidence of cortical perivascularitis, there may be found very marked infiltration around the vessels of the base of the brain and the perforating arteries and their ramifications.

It is often difficult to distinguish lymphocytes from the proliferating nuclei of glia cells. We may distinguish three kinds of lymphocytes in transverse sections of blood-vessels and the surrounding tissues: (1) Hyaline forms, in which the nucleus is pale, staining poorly, irregular in outline or lobulated, and with a small amount of cytoplasm. (2) Small mononuclear cells in which the nucleus is irregular in outline or round, staining either deeply throughout, or the chromatin is arranged in the form of a wheel, with a central nucleolus, from which straight spokes pass out to a nuclear membrane ending in little knobs; there is hardly any surrounding cytoplasm. (3) Large mononuclears possessing phagocytic functions, the main difference from the smaller variety being the much larger amount of surrounding cytoplasm; they form the so-called plasma cells, and are developed from the proliferating endothelial plates, the same as the smaller lymphocytes; the latter can develop into them (*vide* Plate I, fig. 1). Whether an endothelial plate will form small or large mononuclear cells apparently depends largely upon the number of nuclei the original nucleus divides into.

In sections of vessels cut obliquely so that the outermost structure of the wall is shown—that is, the part in contact with sleeve of cerebrospinal fluid—I have seen endothelial cells lying like scales on the bark of a fir tree, or a tessellated pavement, and presenting all the appearances of the typical plasma cells of Marscholko. It appears to me a mere

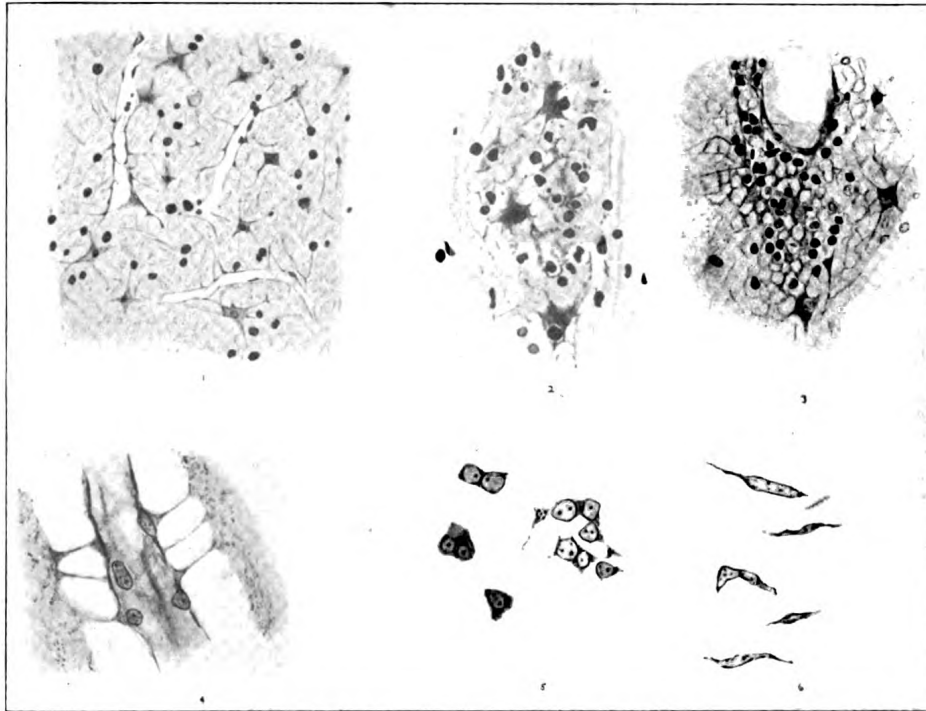


PLATE III.

NEUROGLIA, HYPERPLASIA, AND PROLIFERATION, &c.

- FIG. 1.—Section of subcortical white matter of the brain of a monkey that died after infection by trypanosomes, caused by the bites of infected flies. There is little or no perivascular infiltration, but a considerable increase in size and number of the perivascular glia cells. The animal lived only eight months. ($\times 320$.)
- FIG. 2.—Section of subcortical white matter of a monkey that died eighteen months after infection, and showed the characteristic perivascular infiltration, with lymphocytes and plasma cells. The neuroglia proliferation is well shown, and in the meshwork of the branching fibres, which form a reticulum around a small vessel in longitudinal section, are numerous lymphocytes. ($\times 450$.)
- FIG. 3.—Transverse section of a blood vessel, with the pia-arachnoid and lymph-sheath much increased by proliferating cell elements. The lymphocytes are pale and unstained, and fill the connective-tissue meshwork. The neuroglia cells are seen externally, sending their processes inwards to join the connective-tissue reticulum of the pial sheath. ($\times 375$.)
- FIG. 4.—Small vessels of brain of a monkey in which experimental anæmia had been produced by ligature of all four arteries. This is to show the perivascular space filled with cerebrospinal fluid. The supporting trabeculæ are well seen passing across from the nervous matter to the wall of the vessel. It is easily to be understood that if this sheath is filled with cells entrapped in a thickened and proliferated network, the circulation of the lymph and cerebrospinal fluid will be interfered with. ($\times 750$.)
- FIG. 5.—Young neuroglia cells undergoing proliferation. ($\times 375$.)
- FIG. 6.—Red cells (Stäbchenzellen of Alzheimer), rarely met with, although occasionally appearances like this are seen. ($\times 450$.)

quibble whether plasma cells are developed from lymphocytes or endothelial cells, since, in my opinion, there is sufficient evidence to show that both plasma cells and lymphocytes in chronic inflammatory conditions develop from endothelial cells of serous membranes and perivascular lymph structures, and from endothelial plates of the connective tissues.

The Neuroglia.

It is often a matter of some difficulty to distinguish young neuroglia cells from hyaline lymphocytes. By use of the modified Heidenhain and the polychrome and eosin stains, I was able to see all the changes which Watson described in juvenile general paralysis, and just as in that disease neuroglia-cell overgrowth is a leading histological characteristic, so it is of sleeping sickness and chronic trypanosome infections. The young neuroglia cells may be recognized by their pale-staining round or oval nuclei with a delicate intranuclear network containing one or two small nucleoli and a definite nuclear membrane. The chromatin substance is stained blue; surrounding the nucleus is a well-defined zone of protoplasm stained pink, of irregular quadrate or polygonal outline. These cells can be seen in groups and undergoing active division, especially in the neighbourhood of the ganglion cells. The various phases in the development of the neuroglia cells can be seen, viz.: (1) The nucleus, surrounded with an indefinite amount of cytoplasm, polygonal or irregularly quadrilateral in shape; (2) the protoplasm tending to form short spike-like processes, sometimes giving it a star-like appearance; (3) increase of cytoplasm around the nucleus and commencing formation and differentiation of the *darkly-stained* Weigert stiff fibrils; (4) further development of the Weigert fibrils and extension of one on to the wall of a vessel, there ending in a foot-like expansion; (5) further increase of development of the Weigert fibrils and differentiation from the pink-stained protoplasm on which they appear to lie; (6) the protoplasm is almost entirely differentiated into fibrils, and the nucleus is shrunken and stains deeply like the fibrils, so that the whole glia cell is stained a deep blue-black.

Distribution of the Glia Proliferation.

The distribution varies in different cases; it is almost entirely a primary interstitial overgrowth and not secondary to neural degeneration. It exists in a marked degree in cases which during life presented

no very marked symptoms pointing to destruction of nervous elements. In some very chronic cases in which there have been many epileptiform seizures, there may have occurred sufficient degeneration in the pyramidal tracts to give rise to a secondary sclerosis, but this is exceptional.

The glia proliferation, which is not visible to the naked eye in sections of the spinal cord, becomes very manifest when examined with a low power, and there is a diffuse glia proliferation, as I first pointed out in the two cases which I first investigated. This diffuse subpial glial proliferation affects the periphery of the cord and spreads inwards along the septa; it is not only met with in the white matter, but is evident also in the grey matter. The situations in the brain where glia proliferation is most obvious in general paralysis are the situations in which it is most obvious in sleeping sickness. Thus it is well advanced in the most superficial layers of the cortex, where large branching cells with deeply-stained Weigert fibrils can be seen forming a subpial felt-work. The large branching cells with Weigert processes extending on to the small vessel walls cannot be seen so well amidst the columns of cells as in the subjacent white matter. From the examination of the brains of two monkeys that died of sleeping sickness after experimental inoculation, the glia-cell overgrowth and extension of processes on to the vessels appeared to be more marked than the perivascular mononuclear infiltration, as if this tissue was the first to respond to the irritation of the noxious agent (*vide* Plate III, fig. 1). However, examination of a case—Mrs. S.—in whom symptoms only existed for two months, did not show a glia proliferation in excess of the mononuclear infiltration; nor could I find any neuroglia proliferation or perivascular infiltration in a chronic case of infection by *Trypanosoma gambiense*, a native of Uganda, who died of pneumonia and pneumococcic meningitis after an illness of ten days, but who, prior to this illness, had displayed no symptoms of nervous affection.

The meningeal and perivascular infiltration with lymphocytes and plasma cells was regarded by Nissl as pathognomonic of general paralysis; but I pointed out that plasma cells as well as lymphocytes occurred in the perivascular infiltrations of sleeping sickness, and I figured the same on p. 289, vol. ii, *Archives of Neurology*, 1903. I mention this because an Italian observer claims to have first described plasma cells in sleeping sickness.

Changes in the Central Canal of the Spinal Cord.

Not only is there evidence of a chronic irritative action of the cerebrospinal fluid by the cell proliferation in the meningeal and perivascular lymphatics, but in all chronic cases the central canal of the spinal cord is filled up owing to a proliferation of the cells of the ependyma. I found that this had occurred in quite juvenile subjects. It was so in the little Congo negro boy who died in Charing Cross Hospital in 1898, and I was of opinion then that this fact afforded evidence of a very chronic nervous affection caused by some irritating agent. Such change denotes, then, a chronic process of considerable duration. Examined under a high power, the nuclei of the cells lining the spinal canal may often be seen undergoing active proliferation, and specimens stained with polychrome and Heidendain-eosin method exhibit large pale nuclei with a thin membrane and chromatin granules stained blue, surrounded by a pink cytoplasm, often with numerous processes. In some very chronic cases the glia proliferation had led to the formation of abundant Weigert fibrils. In the grey matter around the central canal numerous glia cells having a similar appearance can be seen.

I deem it of little importance whether the glia proliferation precedes mononuclear cell infiltration, or whether by its doing so it obstructs the flow of the lymph and entangles the mononuclear cells; nor do I regard it of much importance whether we speak of this formative cell hyperplasia as a chronic inflammatory process or not. The important fact to recognize is that this meningeal and perivascular infiltration is a hyperplastic reaction of fixed tissue elements to a noxious agent—*Trypanosoma gambiense*. So far we are on certain ground. It is, however, a matter of speculation whether this tissue reaction is due to (a) the relatively few trypanosomes which can be demonstrated in the fluid; (b) the elaboration of a toxin by them; (c) a transition to some hitherto undiscovered modified forms.

Changes in the Small Vessels and Capillaries.

The capillaries in the pia and in the brain tissue show the following changes, but these are not nearly so marked as in general paralysis of the insane.

The nuclei of the endothelial cells may undergo proliferation, and in the neighbourhood of the capillaries and small vessels there are often numerous lymphocytes, plasma cells, and glia cells sending a process on

to the wall of a vessel; but I fail to find evidence of sprouting new capillaries as seen in general paralysis, nor can I but very rarely find any evidence of the Stäbchenzellen or rod-cells described by Alzheimer in general paralysis (*vide* Plate III, fig. 6).

The marked proliferation of the vascular endothelium with hyaline degenerative changes of the small vessels so frequently met with in general paralysis is hardly ever seen in even the most chronic case of sleeping sickness, nor can I find any evidence of endarteritis so generally met with in all cases of syphilitic brain disease. There may be a granulo-aqueous degeneration of the lymphocytes and plasma cells in the perivascular spaces, but I have never seen caseation nor have I seen tumour formation. This looks as if the trypanosome when it was surrounded by cells in the perivascular space did not undergo division and multiply because it requires a fluid medium, but was walled in by cells and killed unless it had escaped into the free cerebrospinal fluid. Whereas the growth starting in the meninges and spreading inwards along the pial sheaths as well as superficially suggests that the spirochæte multiplies at the expense of the cells, resulting from the chronic irritation of the endothelial and connective-tissue cells spreading thereby and setting up fresh cell hyperplasia with the formation of lymphocytes and plasma cells; but inasmuch as the walls of the arteries participate in this cell hyperplasia, endarteritis occurs, and this, in conjunction with the rapid neoplastic formation, leads to necrobiosis of the older central portions of the tumour.

Vascular (usually capillary) hæmorrhages are met with in all forms of trypanosome disease, and probably are the result of obstruction by the organism. Hæmorrhages may occur in syphilis, but these are due to arterial degeneration, as a rule, with thrombosis or rupture of the vessel.

Changes in the Neural Elements.

Although the meninges are in many cases obviously thickened and the convolutions flattened (indications of some intracranial pressure), yet there is no naked-eye wasting of the brain. The depth of the grey matter of the cerebral cortex is not appreciably diminished, although the vessels both in the grey and white matter may appear somewhat congested.

I have not observed granulation of the ependyma of the ventricles, so characteristic of the meningo-encephalitis of general paralysis of the insane. Moreover, the marked wasting of the grey matter of the

cerebral cortex, so characteristic of the disease, is not met with in sleeping sickness. The convolutions are broad and of normal size, and the sulci tend to be obliterated in sleeping sickness, whereas in general paralysis the convolutions are shrunken from atrophy of the neural elements, cells and fibres, and the sulci are consequently broad and deep. In both diseases there is thickening of the leptomeninges and septal and perivascular changes, but here, it seems to me, the similarity ends. But this statement becomes more apparent and convincing when the microscopic changes are described. Moreover, a comparison of the size of the remaining structures of the central nervous system shows that in general paralysis there is a primary neuronc atrophy which does not occur in sleeping sickness. Thus to the naked eye the spinal cord in the latter disease may appear normal as regards amount of grey and white matter, whereas in general paralysis the cord is often much reduced in size and there is very obvious neuronc atrophy.

The naked-eye appearances therefore point especially to a primary parenchymatous degeneration in general paralysis with chronic interstitial and meningeal inflammation, whereas in sleeping sickness the morbid change is primarily interstitial and with some secondary parenchymatous atrophy (*vide* figs. 3, 4, 5).

Microscopic Examination of the Nerve Cells and Fibres.

In uncomplicated cases that have died within six months of the onset of the lethargy untreated by organic arsenical preparations, I have found a widespread diffuse infiltration of the meningeal and perivascular lymphatics, especially of the subcortical structures, with comparatively little distortion of Meynert's column or atrophy of cells. In a European who was treated and lived one year, having epileptiform seizures for weeks prior to death, there was a considerable atrophy and destruction of cell elements; but the perivascular and glia change, as compared with general paralysis, was out of all proportion to the neuronc atrophy.

Cells.—The changes in the ganglion cells may be considered as due (1) to the primary lymphangitis, and (2) to secondary microbial toxæmia. It is difficult to differentiate the cells which are affected by the one cause from the other. I consider, however, that the chronic change is indicated in those cells in which (1) there are appearances of atrophy of the dendrons, the protoplasmic processes being either attenuated or broken off; (2) there is a perinuclear chromatolysis, the cytoplasm still exhibiting some remnants of a pattern of Nissl granules in the circum-

ference of the cell and on the dendrons; (3) the nucleus is large and clear, and often eccentric. Sometimes a dead ganglion cell may be seen being devoured by phagocytes. The cells of the spinal cord usually show much less change than the cells of the medulla oblongata and the cerebral cortex. The cells of the posterior spinal ganglion usually show chromatolysis, but not destruction (*vide* Plate IV). The appearance of the cells in acutely fatal trypanosome affections—e.g., surra and jinga in animals—could be accounted for by the anæmia caused by the blood change and the obstruction of the small vessels by the trypanosomes. In the brain of a rabbit dying of surra one month after inoculation, the ganglion cells all showed a shrinking of the cytoplasm, a marked chromatolysis and disappearance of the Nissl granules and swelling of the nucleus, and a change not unlike that observed in some forms of experimental anæmia.

Fibres.—In cases uncomplicated by terminal microbial infection, there is a certain amount of fibre atrophy proportional to the cell atrophy described. This atrophy is most obvious in the tangential layer of the cortex cerebri, where the fibres in places are greatly diminished, or even absent. There may also be some diminution of the fibres in the super-radial and inter-radial systems, especially in chronic cases. There is, however, in the brain as in the spinal cord, no definite system tract sclerosis, the result of atrophy of a neuronic system. Generally in the lateral columns corresponding to the pyramidal systems some degenerated fibres can be seen by the Marchi method, but the glia proliferation tends to follow the distribution of the septa rather than to accord with any definite atrophy of a system of nerve fibres. By the Marchi method, the cerebrum, cerebellum, spinal cord, and spinal ganglia were examined in a number of cases. In most instances the results were unsatisfactory, owing to a generally diffuse blackening of the myelin sheaths and the deposition of black granules. I consider that this change was probably the result of acute changes in the myelin, brought about by terminal microbial toxæmia, fever, &c. Some few of the cases, however, did not show this generalized change in the myelin, and a certain number of fibres showing Wallerian degeneration were found. These changes we may regard as definite, and indicative of neuronic decay.

EXAMINATION OF NERVOUS TISSUES OF ANIMALS EXPERIMENTALLY
INFECTED BY TRYPANOSOMES.

Experimental Evidence.—Animals inoculated with *Trypanosoma gambiense* usually die before the characteristic lesions of the nervous system can occur. I have examined the tissues of nine animals (monkeys) which were inoculated at Entebbe in one way or another with *Trypanosoma gambiense*. They were all said to have exhibited the characteristic lethargy, but it is very difficult to differentiate (according to my experience) between a monkey that sits moping when profoundly ill and an animal which exhibits a lethargy on account of the brain lesion.

The tissues of the brains of all the animals sent to me, with the exception of two, showed no characteristic change. The vessels of the brain were empty and there was no meningeal or perivascular infiltration. Several of these animals had survived the infection (as proved by the existence of trypanosomes in the blood) one year. One was subsequently infected with diplo-streptococci from a case of sleeping sickness; yet there was no sign of the meningo-encephalitis met with in every case of human sleeping sickness. This was the experience, apparently, of Ayres Kopke.

The tissues of two monkeys inoculated with *Trypanosoma gambiense* showed, however, the characteristic lesion of human sleeping sickness. I have examined portions of the tissues, and find that there is a very marked neuroglia proliferation of the perivascular lymphatics, endothelial cell proliferation and lymphocyte accumulation, and a few plasma cells around the vessels of the brain in all the situations examined. In fact, the lesion in no respect differs essentially from that of human sleeping sickness.

A correlation of the clinical notes of thirty cases of sleeping sickness before the treatment by organic arsenical preparations was introduced, with a microscopic investigation of the changes in the central nervous system, shows that there is a parallelism between the intensity of the chief nervous symptoms—viz., drowsy lethargy, mental enfeebleness and fatigue, paresis and tremors—and the generalized chronic diffuse meningo-encephalitis. The general intense perivascular infiltration with lymphocytes and plasma cells must interfere with the circulation of the ambient fluid of the neurons, whereby they suffer from an insufficiency of oxygen. The fluid which circulates in the perivascular lymphatics is the ambient fluid that takes oxygen from the blood to hand it over to the nerve

cells. This progressive, universal, and intensely inflammatory state of the perivascular lymphatics would interfere with its flow and lead to deficient oxygen supply. There is an interference with the outflow of the cerebrospinal fluid, but not sufficient to produce a choked disk, so that, although this may tend to produce cerebral anæmia, it cannot be so important a cause of the functional defect of the neurones, and yet it may take part in the production of the symptoms. The principal cause of

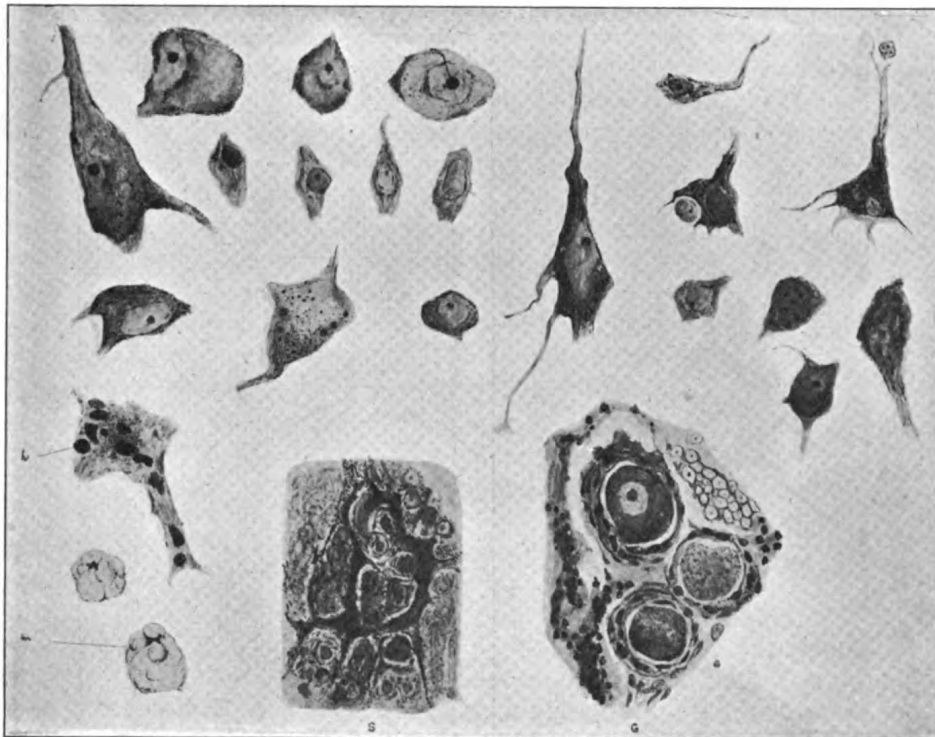


PLATE IV.

CHANGES IN THE CELLS OF THE CENTRAL NERVOUS SYSTEM.

Appearance of various large and small pyramidal cells of the cerebral cortex in advanced cases of sleeping sickness, showing various degrees of chromatolysis, eccentric position of the nucleus, breaking off and disappearance of the processes.

The cell (*h*) is obviously dead and being devoured by phagocytes. Below this are two granule cells (Körnchenzellen). ($\times 375$.)

FIG. *S* is a section of a posterior spinal ganglion, showing an intense interstitial lymphatic-cell infiltration with lymphocytes. ($\times 90$.)

FIG. *G* shows a portion of the section of the same more highly magnified. Not only can the interstitial lymphatic-cell infiltration be observed, but there is a proliferation of the endotheelial cells of the capsule. ($\times 375$.)

the lethargy, in my judgment, is the perivascularitis. Moreover, a vicious circle is established, for the more these lymphatics become obstructed by the actively growing young cells, the more the oxygen that may be in the fluid will be snapped up by them and the less will be at the disposal of the neurones. Consequently, the oxygen supply necessary for functional activity of the nerve cells becomes progressively less and the drowsy stupor deepens proportionally. The experiments of Verworn prove the importance of oxygen storage by the nerve cells and

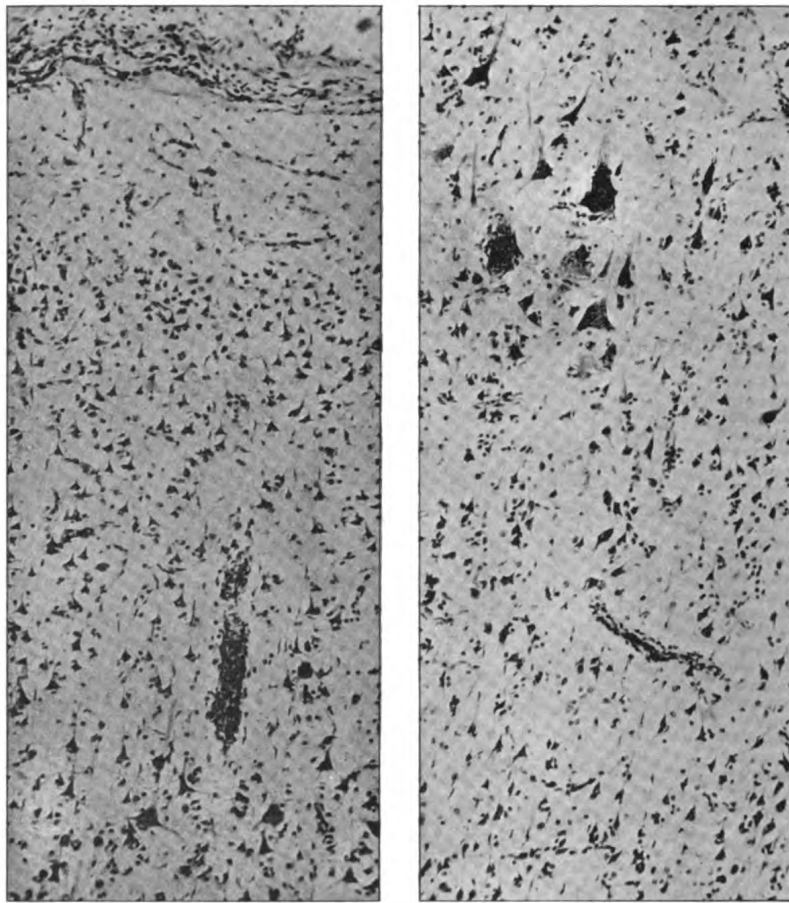


FIG. 3.

Photomicrograph of the cortex from a case of uncomplicated very chronic sleeping sickness. The pyramidal cells are not destroyed; there is not any increased vascularity; there is some perivascular and meningeal infiltration, not nearly so marked as in the subcortical tissue. The columns of Meynert are not disorganized; this accords with the fact that the main symptoms were paresis, tremors, drowsy lethargy, but no epileptiform seizures or mental disturbance beyond enfeeblement. ($\times 150$.)

the necessity of its supply for functional activity. In widespread generalized syphilitic meningitis and perivascularitis a drowsy stupor is a frequent symptom; in general paralysis the perivascularitis may be very intense in the cortex, but never so diffuse and intense in all the sub-cortical structures as in sleeping sickness. The progressive dementia which is the characteristic of the former disease is proportional to the atrophy and wasting of the cortical substance—a condition which is not usually met with in sleeping sickness. In juvenile general paralysis the primary parenchymatous change is more manifest because convulsive

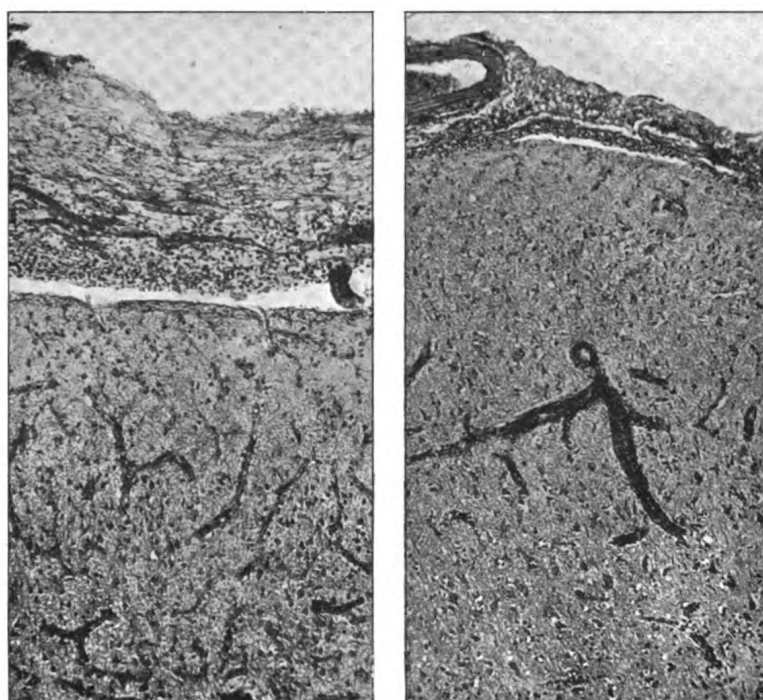
*a*

FIG. 4.

b

Two sections of the cortex in general paralysis; thickening and infiltration of membranes, perivascular infiltration, formation of new vessels and marked atrophy of cortical substance, especially in *b*, the frontal region; *a* is the post-central region. (\times *a*, 120; *b*, 75.)

seizures are less frequently met with. I have observed two forms of change in the cells in general paralysis—viz., an atrophic change and an acute swelling accompanied by chromatolysis similar to that observed in experimental anæmia. This change is doubtless due to vascular stasis and accounts for the fact that after prolonged unilateral convulsive

seizures one hemisphere will be found to weigh very much less than the other, and microscopic examination will exhibit acute destruction of nervous elements in the hemisphere opposite to the seizures. If we regard the parasyphilitic affections, tabes and general paralysis, as being due to premature decay of neurones, it is not to be expected that drugs which benefit by killing the organisms will be of any service. Seeing

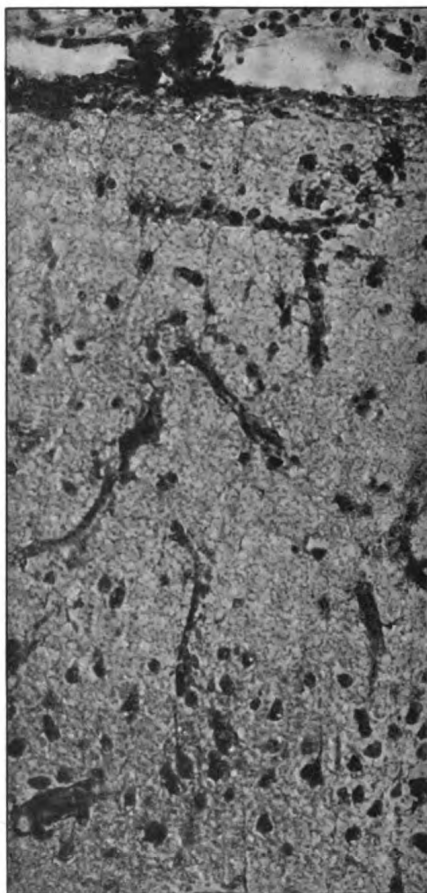


FIG. 5.

Section of the brain of a case of advanced general paralysis, showing the absence of cells in the superficial layer of the cortex. Numbers of vessels are seen to which many glia cells are attached. There is a complete absence of fibres and destruction of the superficial cortical cells (stained by van Gieson method). ($\times 262$.)

that the spirochæte has never been demonstrated either in the tissues or cerebrospinal fluid in these affections, whereas it has in gummatous meningitis, we can understand why mercury, antimony, and arsenic

compounds will, by killing the organism, cure syphilis of the nervous system and will not cure general paralysis or tabes. But why do these drugs have no influence in sleeping sickness? In syphilis the organism has not escaped into the free fluid, for it has never been demonstrated there. To rid the nervous system of the syphilitic organism it is therefore probably not necessary for the drug to get into the cerebrospinal fluid.

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Note upon the Examination, with Negative Results, of the Central Nervous System in a Case of Cured Human Trypanosomiasis.

By FREDERICK W. MOTT, M.D., F.R.S.

(Received October 22,—Read November 3, 1910.)

This is the first case in which “a chance has occurred of examining a cured case of human trypanosomiasis *post mortem*,” according to the statement of C. A. Wiggins, the Acting Principal Medical Officer of the Uganda Protectorate, who has kindly forwarded me the tissues for microscopic examination.

Summary of the History of the Case.—Narain Singh, a Sikh, belonging to the 4th K.A.R. (aged 30 at death), was found to be suffering from trypanosomiasis in June, 1905, and received treatment with inorganic arsenic. The previous history as far as ascertainable, compiled from extracts of reports and history sheets, is published in the full account, but, in brief, it may be assumed that the drug was given intermittently for 18 months or more, and pushed till toxic symptoms of neuritis, mental dullness, etc., rendered further energetic treatment impossible; trypanosomes were then no longer obtained by puncture of the glands. Unfortunately there is no note of lumbar puncture having been performed until a few months before death, therefore we do not know whether invasion of the sub-arachnoid space ever occurred either before or after the treatment. But it is probable that trypanosomes were never present in the cerebro-spinal fluid, for if they were, the symptoms of Sleeping Sickness would, in all probability, have come on, in spite of treatment by atoxyl. Sir David Bruce, in December, 1908 (that is three and a half years after the trypanosomiasis had been discovered), saw this man, and stated that he appeared to be in excellent health. A year later he was seen by Captains Hamerton and Bateman, who reported no symptoms of Sleeping Sickness. They made a very careful investigation of the blood, both by microscopic examination and by experimental injection into monkeys; the results were negative. In June, 1910, lumbar puncture was performed, and 17 c.c. of fluid withdrawn; the centrifuged fluid showed no lymphocytosis or trypanosomes; and injection of the fluid into a monkey was followed by negative results. The patient was attacked with pneumonia in August, 1910, and died three days after admission to the hospital. At the *post-mortem* examination grey hepatisation of the whole right lung was discovered. Beyond fibrosis and induration of the cervical and inguinal

glands there was nothing noteworthy in the appearance of the organs and tissues. The brain was quite normal in appearance, and there was no excess of fluid.

It may be mentioned that this man contracted syphilis on July 27, 1906, and he was treated for some time with mercury, and a note on February 15, 1908, is as follows:—Condition the same as August 6, 1907, but no trypanosomes found in blood or glands, due to fact of taking mercury for syphilis.

Histological Examination.—Sections were prepared of portions of the cerebrum, cerebellum and medulla oblongata, by all the methods which I have previously adopted for the examination of the tissues of Sleeping Sickness cases. I found no trace of the characteristic meningeal and perivascular infiltration, nor of gliosis. Sections of the spleen, liver, and kidney were also examined with negative results.

I have shown that there is a parallelism between the intensity of the signs and symptoms of Sleeping Sickness and the diffuseness and intensity of the lymphatic perivascular infiltration with lymphocytes and plasma cells which is the main cause of the clinical phenomena.

It may be asserted that this case proves that human trypanosomiasis is curable, but it does not prove that Sleeping Sickness is curable, for I contend that the diagnosis of "Sleeping Sickness" can only be made when there is proof that the trypanosomes have invaded the sub-arachnoid space. The case emphasises the importance of early diagnosis of the infection and the value of early energetic treatment by organic arsenic preparations. How far the administration of mercury assisted to complete the cure is uncertain.

UGANDA PROTECTORATE.

DEATH REPORT.

Entebbe Station, August 17, 1910.

Name.	Nationality.	Age.	Sex.	Date of admission.	Date of death.	Disease for which admitted.	Cause of death.	Place of death.
Narain Singh, No. 4662 I.C. 4th K.A.R.	Sikh	30	Male	3.8.10	6.8.10	Bronchitis	Pneumonia	Indian Contingent, 4th K.A.R. Hos- pital.

Previous history as far as ascertainable, compiled from extracts of reports and history sheets :—

22.6.05. Trypanosomiasis. Received treatment inorganic arsenic.
4.12.06. Gland puncture. Trypanosomes +.

Four injections 2 c.c. atoxyl 20 per cent. December 6, 7, 16, and 17.

18.12.06. Glands trypanosomes +.

28.12.06. Glands trypanosomes -. Atoxyl 20 per cent., 2 c.c.

29.12.06. Repeated atoxyl 20 per cent., 2 c.c.

30.1.07. Glands trypanosomes -.

8.2.07. Glands trypanosomes -.

Condition.—Arsenical neuritis. Drowsy looking. Rheumatic pains.

6.8.07. Condition far from satisfactory. Irregular fever, rapid pulse. Dull and stupid. Cervical glands enlarged. Trypanosomes not found in glands since March, 1907. Energetic treatment with arsenic impossible owing to symptoms of poisoning rapidly appearing.

15.2.08. Condition the same 6.8.07, but no trypanosomes found in blood or glands, due to the fact of taking mercury for syphilis (contracted 27.7.06).

16.12.08. *General Condition.*—Strong, well nourished. No tremors. Reflexis normal. Gland puncture and blood examination trypanosomes -.

Differential count. Lymphocytes 70 per cent.

Some tendency to drowsiness when unoccupied.

Last treatment, two injections kharsin, May, 1908.

18.12.08. Proceeded to Mpumu to do duty with the Royal Society's Sleeping Sickness Commission. Report by Sir David Bruce—"This man appears to be in excellent health." Returned to Entebbe.

16.12.09.—Report by Captains Hamerton and Bateman, R.A.M.C., Sleeping Sickness Commission, Mpumu—"No symptoms of Sleeping Sickness."

Blood Examination.—Examined peripheral blood. Negative results 14 occasions.

Examined centrifuged peripheral blood. Results negative.

Examined blood from median basilic vein. Results negative.

Examined blood from median basilic vein centrifuged. Results negative.

16.12.09. 4 c.c. blood from median basilic injected into monkey.

29.12.09. 5 c.c. " " " "

1st monkey examined 15 times. Results negative.

2nd " " 12 " " "

13.6.10. Lumbar puncture 17 c.c. Cerebro-spinal fluid abstracted centrifuged. Trypanosomes -. No excess white cells. 12 c.c. injected into monkey. Monkey examined twice weekly over one month. Results negative.

General habits.—Intemperate. Had gonorrhoea and syphilis.

Post-mortem appearances 14 hours after Death.

Body of lean but in no way emaciated man.

Externally.—Cervical glands—small, hard, and shotty. Inguinal glands—small, hard, and shotty.

Chest.—Parietal and visceral pleura adherent right side, due to recent pleurisy.

Right Lung.—Weight 58 ozs. On section the whole lung was in a state of grey hepatisation.

Left Lung.—Weight 14 ozs. Pleura and lung substance normal.

Heart.—Weight 12 ozs. Right heart distended with blood clot. All chambers and valves normal. The glands at the root of lungs and around bronchi and trachea were enlarged and soft, and some were purulent.

Microscopic.—Examination of this pus showed organisms resembling pneumococci.

Liver.—Weight 89 ozs. Enlarged and congested. On section, soft and friable. Probably some fatty change. No obvious fibrotic changes.

Portion preserved for microscopic examination in England.

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Spleen.—Weight 14 ozs. Feels hard to the knife on section. Pale appearance and excess of fibrous tissue on cutting open.

Portion preserved for microscopic examination in England.

Kidneys.—Right, weight 5 ozs. Left, 6 ozs. Both were swollen, the kidney substance bulging from the capsule when cut into.

Both capsules were a little adherent.

Cortices undiminished. The whole kidney substance appeared a little paler than normal.

Portions preserved for microscopic examination in England.

Pancreas and Suprarenals.—Normal.

Stomach.—Slightly dilated. No gastritis. Some *post-mortem* staining.

Intestines.—Normal. Mesenteric and retroperitoneal glands not enlarged.

Brain.—Calvaria normal. Weight of brain, 52 ozs. No thickening of membranes. Brain substance normal. Ventricles normal in size and no excess of fluid.

Portions of cerebral cortex and cerebellum preserved for examination in England.

(Signed) H. B. OWEN,
Medical Officer, Civil Hospital, Entebbe.

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March, 1911.]

SEVEN CASES OF AMAUROTIC IDIOCY (TAY-SACHS DISEASE).

By HILDRED B. CARLYLL and F. W. MOTT, F.R.S.

PART I.—BY DR. CARLYLL.

AMAUROTIC family idiocy is a name which has been given to a rare disease of the nervous system occurring in Hebrew children. For these reasons a practical knowledge of the disease, as regards clinical symptoms and diagnosis, can be possessed only by a few; and, further, the objection raised by the Jewish race to autopsies increases the difficulty of obtaining material for systematic pathological research.

The clinical symptoms of the disease are so characteristic that, if borne in mind, no difficulty in diagnosis should occur; indeed, the pathology is so distinct as to indicate a correct diagnosis.

In recent years, as knowledge of the disease has increased, many accounts of cases, partial or complete, have been published; so that a correct diagnosis is now arrived at more frequently. As yet, however, the majority of text-books contain no adequate account of this interesting disease. It is therefore with no apology that I put on record the notes of six cases which have come under my personal observation during twelve months' residence at the East London Children's Hospital, together with those of a case recently under Dr. Mott's care. That the details of some of these cases are incomplete will be evident to the reader, but I trust that the shortcoming may be condoned when it is remembered that in these alien families the details of the medical history had frequently to be obtained through an interpreter.

2 Carlyll & Mott: *Seven Cases of Tay-Sachs Disease*

My six patients are not akin to one another, but an elder brother of the first child whom I saw suffering from the disease had died three years before of the same complaint. His case, with another under Dr. Mott's care, was published in detail by Dr. Mott in the third volume of the *Archives of Neurology*, and I shall draw from the notes of that case for purposes of comparison with those of his sister (Case I). Case VII is a patient that recently came under the notice of Dr. Mott at Charing Cross Hospital, and, with his permission, I have included the history with my series of cases.

One of my patients (Case IV) came under observation in an interesting way. The mother of the two children mentioned above, a woman of unusual intelligence, noticed this child in his mother's arms in a tram-car. A rapid inspection convinced her that the child could not see, and she quickly came to the conclusion that his state was identical with that of her own children. The child's mother was so impressed with the statement that her baby could not see, which fact she had not discovered for herself, that she readily consented to bring him to the hospital.

The seven patients are all children of Jewish patients, coming from Russia or Poland. Some of the children were born abroad, others in England. Five cases are of girls, two of boys. Another member of the family of my first patient (Case I) died of the disease; and in Case III there are reasons to suppose that the only other child of that family may have died of the same affection. The youngest child in the family of which the patient (Case II) was a member presents certain very suspicious symptoms, and will be kept under observation.

All the children have now succumbed and their ages at death were as follows :—

Case I, 2 years 3 months.	Case IV, 2 years 3 months.
„ IA, 12 months.	„ V, ¹ 13 months.
„ II, 2 years 4 months.	„ VI, ¹ 18 months.
„ III, 1 year 8 months.	„ VII, 17 months.

Dr. Mott's other case, reported in the third volume of the *Archives of Neurology*,² died at the age of 2 years.

In the light of these figures, and of those of other published cases, it is justifiable to tell the parents that children with this affection will not reach the age of 3 years. In none of the families from which these cases are taken is it recorded that the firstborn children were afflicted with the disease (except in Case III).

¹ These cases have died since this paper was written.

² *Arch. of Neurol.*, 1907, iii, p. 218.

In Case I and in Case 1A the fourth and fifth children of the family were affected.

In Case II the patient was the fourth child of the family.

In Case III the second child was affected (the first child is now known to have died from the disease).

In Case IV the patient was the second child of the family.

In Case V the fourth child was affected.

In Case VI the third child was affected.

In Case VII the seventh child was affected.

In every case (except Case III) the patient had healthy brothers or sisters.

In the case of Jenny M. (Case I) the mother sought advice as to whether she would be wise in having any more children or not. She was told there was no reason to believe that her next child would be afflicted.

CASE I.—JENNY M.

Under the care of the late Mr. Hancock at the East London Children's Hospital, 1909.

Family history: Parents alive and well. They are Jews, the father coming from Russia and the mother from Poland. They reside in Spitalfields. No consanguinity. When married, father was 18 and mother 17 years old. The patient is the fifth child of the marriage. The eldest child died at 8 months, of diarrhoea. The second child is now 8 years old and is well. His eyes have been examined and nothing abnormal was detected. The third child, a girl, died of pneumonia when a baby. The fourth child, a boy, afflicted with amaurotic idiocy, died at Shadwell at the age of 12 months (Case 1A). The fifth child is the patient. No miscarriages. The parents have decided not to have any more children.

Mother's family: The mother's parents are alive and well. No consanguinity. She is one of seven children, of whom three are dead, the cause being unknown. One of her brothers is married, but has no children; her other brother has had four children, who are all healthy.

Father's family: There is no information about the father's grandparents; his parents are alive and well. No consanguinity. He has two brothers and seven sisters; of the latter, one died at the age of 3 years from croup, and one after living a few weeks. The remaining five are between 12 and 22 years of age; they are healthy; none are married. Of the two brothers, one is married and has two children who are well, the other is 6 years old.

4 Carlyll & Mott: *Seven Cases of Tay-Sachs Disease*

History: Full-time child, no instruments; breast-fed up to eleven months. The mother, a very intelligent woman, brought her to see Mr. Hancock when she was 4 weeks old because she thought the child was "going like Jack." When the child was 3 months old the mother brought her again, as she noticed that she was partially blind. (Mr. Hancock found the typical ophthalmoscopic signs.) She noticed also that the limbs were stiff because she had difficulty in powdering the groins. The child cried less than other children and did not take any notice of things. From birth she never recognized the difference between the mother who nursed her and other people who lifted her up; nor did she ever play with toys. The general health for twelve months was fairly good, but gradually she got thinner and took her food badly. She always lay quietly where she was put, and the power in her limbs rapidly decreased.

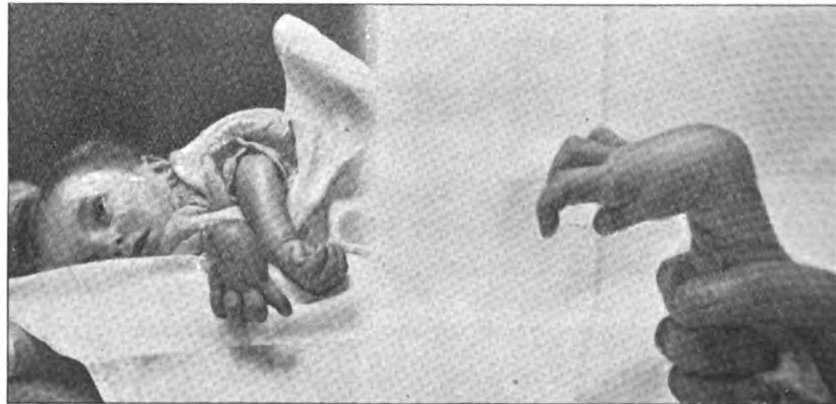


FIG. 1.
July 9, 1909.

Case I.—Jenny M.

FIG. 2.
July 9, 1909. Showing the early
"main en griffe."

On admission, January 9, 1909, aged 1 year and 4 months (the following meagre notes are all that are obtainable): Well nourished and plump. Takes very little notice of people or surroundings, and appears only to eat and sleep. Heart and lungs normal. No convulsions. No strabismus nor nystagmus. Limbs spastic. Weight, 19 lb. 11 oz.

Progress: There are, unfortunately, no notes about her progress; but I am told that the child became progressively thinner, and that nasal feeding became necessary about May. In July, her weight was 14 lb., and the photographs taken then show the hyper-pronation of the left

forearm. On the right side, the hand has assumed a position of "main en griffe" (figs. 1 and 2).

November 9: Always lies in a semi-comatose condition; eyes continually open; pupils dilated, reacting slightly to a strong light. The eyelids sometimes blink, and the eyes are at times withdrawn from a bright light. Optic atrophy marked. Usually there is a slight internal strabismus of recent date. The mouth is kept shut, but can be moved well. There is a slight sucking reflex. The child seems insensitive to sound; head retracted; back considerably bent with scoliosis and kyphosis. Right side: Arm kept slightly from the body and extended at elbow; forearm fully pronated; wrist acutely flexed, and has sore places on dorsum. Fingers hyper-extended at metacarpo-phalangeal

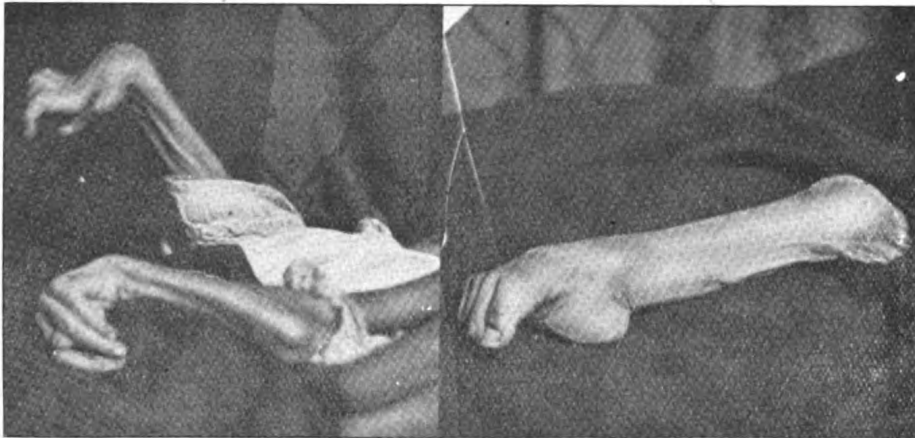


FIG. 3. Case I.—Jenny M.

FIG. 4.

November 12, 1909 (a few hours before death). Note the difference in the deformity of the two limbs.

November 12, 1909.

joints, and flexed elsewhere; thumbs fully adducted and slightly opposed; slightly flexed at metacarpo-phalangeal joint and extended at the inter-phalangeal joint. Leg flexed at hip and knee; sores present over knee; foot and toes plantar flexed to the fullest extent. Left side: Arm slightly flexed at elbow; forearm hyper-pronated; leg straight at hip and knee; position of foot as on right side. These contractures are well shown in figs. 3 and 4. Abdomen very lax; no enlargement of liver or spleen. The plantar reflex is extensor on each side, as exemplified by a slight straightening of the great toe. Deep

reflexes not obtained. There is great muscular wasting. The position of the joints can be altered by force, but they tend to return to the original position, except in the case of the right knee, the muscles of which are very weak and lax, so that the joint can be placed in any normal position. There are numerous pressure sores all over the body. Urine and fæces are passed in the bed. Nasal feeding has been employed for five or six months. There have been several slight attacks of bronchitis. The temperature has been normal throughout, except for some terminal pyrexia.

November 12, 1909: The child died, aged about $2\frac{1}{4}$ years.

Immediately after death had occurred the eyes were removed and placed in fixing solutions. The brain was removed later and hardened in Müller's fluid, and subsequently examined by Dr. Mott. No further examination was permitted.

CASE IA.—JACK M.

This child was under the care of Dr. Eustace Smith, Dr. Coutts, and Mr. Hancock at the East London Children's Hospital, in 1906. Dr. Mott performed the autopsy, and has published the result of his chemical and histological examination in the *Archives of Neurology*, iii, 1907. With his permission, and as the second case in the family (Case I) has recently proved fatal, I give his notes here for comparison:—

Family history: *See Case I.*

History: Quite healthy at birth. Normal confinement. No urine passed for twenty-four hours. When six months old the child developed a rash which lasted four or five days. Soon afterwards he developed pneumonia, being dangerously ill for a week. Since this illness he has not noticed things, and his mother thinks this may be due to deafness. His attention cannot be attracted. The eyes wander aimlessly. The mother thinks he should hold his head up better for his age. He has had an aural discharge for five months. No squint. Breast-fed always; no other food; bowels regular. Has never walked nor crawled, but at 6 months old could stand firmly on his legs when allowed to do so. No definite paralysis. The back muscles appear to be quite strong. At six months old the child was taken to the Moorfields Eye Hospital. He was admitted, but having contracted measles, was discharged shortly afterwards.

On admission, January 13, 1906, aged 8 months: Weight, 20 lb. 10 oz. Very well nourished, rather pale. Head of good shape; fontanelle widely open; no cranio-tabes; hair normal. Eyes wander

aimlessly. Attention appears to be attracted, however, by the ticking of a watch, and he looks for it in the right direction. When placed in a sitting position his head does not fall about. Muscular development appears to be very good. Skin normal. Sleeps and eats well. A very amiable child. Gastro-intestinal system: Two lower incisors only; tends to protrude tongue like a Mongol. Abdomen large; spleen and liver not felt. Bowels usually regular; stools normal. Thorax: Well covered, good shape; nothing abnormal in heart or lungs. Nervous system: Cranial nerves intact; pupils equal in diameter; normal reactions direct and consensual; eye movements good in all directions; no nystagmus nor strabismus; no paralysis nor muscular wasting. Reflexes normal for child's age. Fundi present characteristics of the disease.

Discharged January 25, condition "in statu quo."

Re-admitted February 7, 1906, suffering from pneumonia, following what was said to have been measles, but which was probably scarlatina. Very weak. Still well nourished. Neck muscles now obviously weak, causing head to fall back; no rigidity; no obvious muscular wasting; reflexes are still brisk; plantar reflex extensor; eyes are unchanged; well-marked signs of broncho-pneumonia.

February 18: Has been in a critical condition, but signs in lungs are now clearing up. Reflexes brisk. Head muscles weaker, but can move head a little from side to side.

February 24: Still some bronchitis. Right arm now appears to be rigid. Desquamating freely.

February 26 to March 10: Temperature is very irregular, reaching 103° F. at times. Losing weight (14 lb. 14 oz., March 8). Well-marked œdema of hands and feet; semi-conscious. Rigidity of limbs variable. Resents ophthalmoscopic examination.

March 31: Weakness increasing. Temperature subnormal. Profuse hæmaturia. No casts in urine.

April 10: Marked anæmia; skin very dry. Much œdema; abdomen very sunken; skin loose and inelastic; has fits of crying and irritability. Does not know anyone; no hæmaturia; rarely moves limbs, and then only the upper; no vomiting. Eyes nearly always open; they wander aimlessly. Limbs alternately rigid and flaccid. Lower limbs powerless; knee-jerks brisk; Babinski's sign variable.

April 12: Child died suddenly, aged 12 months.

CASE II.—MILLY T.

Under the care of Dr. Eustace Smith in the East London Children's Hospital in 1909. Died at St. George's Infirmary, E., 1910. No autopsy.

Family history: The parents are Russian Jews, and have been in England seven years. They are both strong and well. They have had five children, three older and one younger than the patient. The older children are boys, aged 12, 10, and 5 years respectively (1910). The youngest of the family is a girl aged 8 weeks. I have recently seen this child, and she presents a suspicious similarity to early sufferers from amaurotic idiocy. I was not given permission to examine her eyes. There is no consanguinity between the parents. When they married the mother was aged 20 and the father 24. They do not know of any similar cases of illness in their respective families.

The patient was born at full term without the assistance of instruments, and was brought up on the breast and the bottle.

History: The child was quite well until a year old, when she seemed not to see, and was taken to a hospital. She seemed to notice only bright lights, and could not support her head. At 3 months old she had fallen on her head. Is usually constipated, and has been wasting latterly. Has had no infectious fevers.

Admitted July 8, 1909, aged 16 months. Well developed and well nourished. Skin pale. Weight, 16 lb. General muscular rigidity, especially in arms and legs, which are slightly extended. This stiffness is easily overcome. No head retraction or spinal rigidity. Child lies in a restless condition. Eyes rather fixed, and kept open. Sight seems impaired, but she is not blind, for she turns eyes towards objects presented. (There is no note of an ophthalmoscopic examination.) Cranium well shaped; anterior fontanelle almost closed; no cranio-tabes. Nostrils triangular shaped. Mouth kept open; tongue protruded and often sucked. Abdomen protuberant and rather flaccid. Liver and spleen not palpable. Knee-jerks decidedly exaggerated. No ankle-clonus. Plantar reflex extensor. Lungs and heart normal. Child swallows badly.

Discharged July 14, 1909. Whilst under observation, the temperature ranged continuously from 100° to 102° F. Lumbar puncture revealed a sterile fluid containing a few lymphocytes.

Admitted to infirmary, October 25, 1909, aged 19 months. Weight, 18 lb. 10 oz. The pupils were small and reacted. There was apparently no sight. The face twitched symmetrically. Kernig's sign was marked. There was much salivation.

November 13 : Weight, 18 lb. By the kindness of Dr. Bowlan I was allowed to watch the child's progress.

December 8 : Weight, 17 lb. The child lay where placed, but started at sudden noises. Pale and flabby, features becoming pinched. Much crying. Swallowed fairly well, and did not require nasal feeds. Head fell back when child lifted. Limbs slightly rigid. Knee-jerks brisk. Plantar reflex extensor. Thumbs markedly adducted. Examination of the fundi revealed the characteristic appearances. Lumbar puncture gave a small quantity of fluid under very low pressure. Shortly after this child became worse, limbs being much contracted. Nasal feeds became necessary for a time.

December 26 : Weight, 16 lb. 8 oz.

January 3, 1910 : Weight, 16 lb.

January 12 (*see* fig. 5) : Swallowing well. Pupils react to light. Limbs not markedly contracted, but both hands clenched over adducted thumbs. Plantar reflex indefinite but not extensor. A quantity of fluid was obtained by lumbar puncture.



FIG. 5.

January, 1910. Case II.—Milly T.

The child stayed in much the same condition for several months, becoming more wasted and rigid.

The cerebrospinal fluid (first sample) was alkaline and contained some sugar. Noguchi's test showed an absence of globulin. There were neither cells nor organisms present. Second sample : Protein content normal. Choline test negative. No lipoids beyond a trace of cholesterol present.

July 18, 1910 : Death occurred from pneumonia, following an attack of measles, at the age of 2 years 4 months. No autopsy was allowed, in spite of the most urgent appeals for permission.

CASE III.—FANNY M.

Under the care of Mr. Hancock at the East London Children's Hospital for a short time. Transferred, on account of an epidemic of measles, to the Evelina Hospital in 1909, where she was under the care of Dr. Briscoe. (Owing to Mr. Hancock's death, the child's condition while at Shadwell is not known.)

Family history (1910) : The mother was married once previously in Poland when she was 16 years old. Of this marriage she had one miscarriage. She was aged 24 when she married, in 1904, her present husband. He was 30 years old. No consanguinity. They are Polish Jews, and have lived in England for five years. The mother's parents died when she was a baby. She has one brother, aged 35, who has six healthy children. The father has one sister and several brothers, who have healthy children. The parents have never seen any children with amaurotic idiocy in Poland. They have had two children in all ; the first, a boy (J. M.), was born in Poland, and died in 1907 at the German Hospital, aged 2½ years. The case-notes are not obtainable. He was weakly from birth, and said to 'be rickety. Breast-fed for twelve months. Never used his legs. Became very thin before death. I have seen two photographs of this child, taken at 3 and 12 months respectively. The first photograph shows a fat, intelligent-looking baby with widely open eyes. In the second he is also fat, but presents a rather idiotic look. The limbs appear normal. The mother cannot say anything definite as to his powers of vision, but I think it probable that this child was an amaurotic idiot. The mother agrees that this is probable. (A recent examination of the sections which were prepared when this boy died, leave no doubt that he died of this affection.)

History : Born in England at full term ; large child at birth ; no instruments. Breast-fed to 8 months. Well up to 6 months, when she became weaker and could not hold up her head. When about 8 months old it was noticed that she did not observe things like other children. Sudden noises would start "convulsions."

General condition : The child was sent to the Evelina Hospital on October 7, 1909. She was then 18 months old. Mr. Hancock was anxious to know how she progressed, and I was very kindly allowed to examine her there on November 23, 1909, when her condition was as follows : The face presented a look of dementia, and the child lay where placed. There were no voluntary movements, even when lumbar

puncture was performed; nor did the child cry. No obvious muscular wasting and no contractures were observed. The arms and legs were extended and slightly rigid, but flexion could be performed. Thumbs markedly adducted. Some foot-drop, but this was not well marked. Extensor plantar reflex well marked on each side. Knee-jerks obtained, but not exaggerated. Eyelids sometimes open; no movements of eyes; complete blindness; well-marked optic atrophy. At the macula was a circular area rather larger than the disk, of the colour of dirty cotton-wool, with an ill-defined edge. In the centre of this area was a well-marked liver-coloured spot. The child on admission had taken food fairly well, but for some weeks past had been fed by a nasal tube. Lumbar puncture was readily performed. There was no vertebral



FIG. 6.

Case III.—Fanny M.

rigidity. Two large test-tubes were rapidly filled with clear fluid. Shortly afterwards the child developed chicken-pox, and on December 20, 1909, she died, aged 1 year and 8 months. I was told that no improvement had followed the lumbar puncture (fig. 6). The specimen of cerebrospinal fluid was free of blood, and was not abnormal in cell-content. Reaction alkaline. Noguchi's test showed that it contained no globulin. With Fehling's solution a rapid reduction took place, as is usual with normal cerebrospinal fluids. There was but a small amount of protein. Choline and cholesterol were absent.

Post mortem (December 22, 1909): Well-nourished child. Fontanelle closed. Brain very hard; weight, 33 oz. Ventricles not distended, but a quantity of fluid escaped on opening the skull cavity. Some pus was found in the right pleural cavity.

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Through the kindness of Dr. Briscoe, I was enabled to be present at the autopsy, and to obtain portions of the nervous system and other tissues for pathological research. This was carried out under Dr. Mott's direction, and a portion of the histological and chemical investigations are based upon researches made upon this material (*vide* Part II).

CASE IV.—ABRAHAM C.

Under the care of Dr. Eustace Smith in the East London Children's Hospital, Shadwell, 1908 and 1909. Death occurred in the St. George's Infirmary, E., 1909. No autopsy.

Family history, 1910: Two other children, one aged 6, healthy and at school; the other died of "cough" at 2 weeks old. No miscarriages. The parents come from Russia and have been ten years in England. When they married the mother was aged 20 and the father 22. The mother's parents are alive and well. She has three brothers, aged 12, 10, and 6 respectively, and four sisters. Of these two are married and two are still young. Of the former one has two girls and one boy; the other has one girl. The father's parents are alive; he has brothers and sisters, but nothing is known of them.

History: Full-term child; breast-fed; no instruments. At 3 months old suffered from cramps and constipation; occasional fits. Irritable for two months and suffered from screaming attacks. For two months previous to admission mother had doubted whether he could see properly. A diagnosis of rickets was made at several hospitals.

Admitted to the East London Hospital, October 30, 1908, for bronchitis. Aged 1 year. Weight, 22 lb.; very rickety and unable to stand. Well covered with flesh. Irritable and cries a great deal. Occasional nystagmus; unable to fix objects with eyes. Characteristic appearances seen in fundi. Limbs flaccid. Both knee-jerks brisk. Sometimes a slight ankle clonus occurs. Plantar reflex extensor. Fontanelle normal for age. Liver and spleen not palpable. Four central incisors, two upper and two lower appearing.

Discharged November 9, 1908.

Re-admitted January 30, 1909, for bronchitis following a recent attack of measles. Weight, 15 lb. Child apparently quite unconscious. The only movement is a slight slow rolling of the head from side to side. Slight general rigidity. Eyes half-closed, exhibiting slow lateral conjugate movements; pupils small, equal, and circular; no nystagmus; optic atrophy. Abdomen flaccid and retracted. No œdema.

February 3: Lumbar puncture was followed by a slight improvement. The fluid was sterile and showed a few small lymphocytes, but not in pathological numbers.

February 9: Sometimes swallows naturally but generally requires nasal feeds.

February 19: Gaining weight; total weight now 18 lb. Nasal feeds not required.

Discharged March 8. Some improvement.

Re-admitted October 1, 1909, for the third time. Weight, 20 lb. Has taken food well since last admission. Very constipated. Feet and abdomen said to have recently swelled. Fairly well nourished. Lies on side with head retracted. Eyes open and staring. When disturbed eyes move ceaselessly from one side to the other side with rapid, jerky



FIG. 7.

October, 1909. Note the claw hand. Case IV.—Abraham C.

movements. Pupils do not react to light. Legs extended at knee and ankle, but slightly flexed at hip-joints. Plantar reflex flexor; the stimulus usually gives rise to slight clonic spasm of arms and legs, as does any movement of the legs. Knee-jerks increased. No genuine patella or ankle clonus. Arms slightly flexed at elbows; wrists flexed; claw hands. Joints are resistant to passive movement, but on continuing it they become relaxed, and complete flexion and extension can be obtained. The usual position of the joints is, however, quickly resumed (fig. 7).

Discharged October 17, 1909.

Admitted November 2, 1909, to the St. George's Infirmary. By the courtesy of Dr. Bowlan I was permitted to examine the child on

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December 8. Shortly after admission he had convulsions associated with œdema of the legs. He swallowed well and cried but rarely. It was thought that at times he recognized his mother. The head and arms could be moved by the child. The legs were kept extended and rigid. Plantar reflex flexor. Kernig's sign not marked. Well-marked "claw" position of right hand only. Thumbs on each side much adducted and opposed. Eyes showed bilateral movements. Lumbar puncture was performed, but the fluid was not found to be under any pressure. It contained some blood, was alkaline, and contained sugar. Choline and cells absent.

Death, Christmas, 1909. Age about $2\frac{1}{4}$ years.

CASE V.—HARRY K.

Under the care of Dr. Coutts at the East London Children's Hospital, 1910.

Family history: The parents are Russian Jews and are alive and well. They were not related before marriage. They came to England in 1903. There are three other children, a boy and two girls, aged 8, 5 and $2\frac{1}{2}$ years respectively; all alive and well. No miscarriages. The father is one of seven children; his parents are alive. The mother is one of four children; her parents are dead. I can find no evidence pointing to other cases of the disease in this family.

History: The child was born at full term and without difficulty. He was brought to Hospital because his back was weak, and because his mother thought he was "not like other children."

On admission, July 12, 1910, aged 9 months: Weight, 17 lb. Well nourished; pale; does not look intelligent. Fontanelle not closed. Plenty of hair. Circumference of head $18\frac{1}{2}$ in. Has difficulty in sitting up. Is at times sensitive to sudden noises. Takes food well. Nothing abnormal in chest. Abdomen full and lax; nothing abnormal felt. No teeth. Long eyelashes. Cranial nerves intact. Eyes of oval shape, usually open and staring; no lateral movements; no strabismus. The fundi present a typical picture. The pale area at the macula is about one and a half times the size of the disk. Optic disks show early atrophy (Mr. F. Juler). The arteries are small. The pupils react strongly to light. The child sees objects and follows them with his eyes, but has no sense of their position when trying to grasp them. There is no head retraction, but the neck muscles are very weak. The legs are extended and are spastic, but not markedly so. Knee-jerks very brisk. Kernig's

sign indefinite. The feet go into clonus on stimulating the soles, but the legs are only sluggishly moved. The arms move freely at will, the elbows are rigid and flexed. A Pirquet's reaction was positive.

July 20: A test-tubeful of fluid, flowing under considerable pressure, was removed by lumbar puncture. A specimen of blood was removed from the brachial vein.

July 25: There was no pyrexia after the lumbar puncture, but the rigidity was for a time less marked. The operation wound on the arm healed by first intention. The cerebrospinal fluid showed an absence of choline and cells. There was no excess of protein. The amount of



FIG. 8.

July 19, 1910. Case V.—Harry K.

carbonates and carbon dioxide in solution was not altered. Cholesterol was absent. There was no excess of lipoids or fats.

August 26: Weight, 16 lb. Temperature normal. The child lies precisely where it is put, however uncomfortable the position. He is almost ridiculously good for his age, rarely crying, and then only on the greatest provocation. He usually looks about him with widely open, staring eyes, which produce an absurdly vacant expression. He grunts with pleasure when he is spoken to, and frequently bursts into laughter. It is evident that he does not recognize his mother. Perception of light and of bright objects is fairly keen. No squint nor nystagmus; pupils

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react strongly to light. Mouth almost always open; tongue is protruded sometimes. On being sat up, the weakness of the back muscles is evident; but if the head is pushed backwards, as it is very readily, the child can bring it forward to a flexed position. The arms are flexed at the elbows, and are constantly moving. The forearms are strongly pronated. The thumbs are adducted and opposed, and the fingers are kept flexed. Legs somewhat spastic; knees kept extended; thighs are adducted and forcible abduction causes pain and reveals the muscular rigidity. The plantar reflex is flexor; knee-jerks easily obtained, but not very exaggerated. The legs are not moved away from painful



FIG. 9.

July 28, 1910. Case V.—Harry K.

stimuli; they fall helplessly on being lifted. The child takes food well, but will not be bothered with a bottle. The bowels are regular; stools and urine normal. (See figs. 8, 9, and 10).

October 1: Weight, 14 lb. 12 oz. Hands pronated and thumbs tucked in. Fingers move readily at will. Knees extended; no equinus; plantar reflex flexor; jerks readily obtained. There is some difficulty in swallowing at times, but nasal feeds are only occasionally needed. The child has no teeth. The general weakness has increased. On placing salt upon the tongue the child does not cry, but makes a slight grimace.

At times there are outbursts of vacant laughter. Pin-pricks do not readily cause crying. The pupils react slightly to light.

The child was removed by the parents from the hospital on October 31, 1910. Weight, 14 lb. The child died suddenly on November 4, 1910, possibly from some accident while being fed. No autopsy was permitted.



FIG. 10.

August 24, 1910. Note the results of weakness of the neck muscles.
Case V.—Harry K.

CASE VI.—SARAH G.

In the Queen's Hospital for Children, 1910, under the care of Dr. Bellingham Smith, to whose courtesy in allowing me to admit the child for a time in the East London Children's Hospital, and to photograph her, I am much indebted. (This child was shown at the Royal Society of Medicine by Dr. Bellingham Smith in May, 1910.)

Family history: Patient is the third child of Polish Hebrews. The parents are alive and well. They were married in 1902, and have lived

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in England for five years. No miscarriages. According to the history, the two elder children, a boy and girl, aged 7 and $4\frac{1}{2}$ years respectively, are both healthy, and this is corroborated by a photograph of them which I was shown. The father is one of seven children, two of whom died in early childhood. One of his brothers is consumptive. He has a step-brother and four step-sisters. The mother is one of eight, of whom one died at the age of 3 years. Two of her brothers have two children each, but she is unable to say anything as to the state of their health.

History: The child was brought to hospital for blindness and inability to sit up. She could not hold up her head. She has always been breast-fed. The symptoms had only been noticed for a month prior to admission, namely, when the child was 10 months old.



FIG. 11.

July, 1910. Case VI.—Sarah G.

On admission, April 27, 1910, aged 11 months: The child is exceedingly fat and well nourished; very apathetic; unable to sit up without assistance, but on doing so, is unable to support her head unaided. No movements of head or body are attempted, and those of the limbs are limited in character. The limbs are rigid to a variable degree, spasticity being more marked in the legs than in the arms. Plantar reflex flexor. The tongue is protruded. The appearance of the eyes is typical on ophthalmoscopic examination. Optic atrophy is fairly advanced, and the pale area at the macula is rather larger than the disk. There is no nystagmus, but the eyes exhibit aimless random movements. There is distinct appreciation of a strong light, but no notice is taken of surrounding objects. The Wassermann reaction and the Pirquet cutaneous reaction were negative.

July 18, 1910 (*see* figs. 11 and 12): Age, 14 months old; weight, 17 lb.; very plump; has two lower incisors; limbs very spastic; legs and arms being about equal in this respect; unable to sit up; plantar reflex definitely flexor; pupils do not react to light. After a lumbar puncture, at which some cerebrospinal fluid under pressure was removed, there was a pyrexia. The rigidity did not in any way decrease. Perception of light is slight. The pale area at the macula is smaller, and the liver-coloured spot larger than in Case V.

The child died in the autumn of 1910.



FIG. 12.

Case VI.—Sarah G.

CASE VII.—P. P.

Female, aged $1\frac{1}{4}$ years. Admitted to Charing Cross Hospital under the care of Dr. Hunter for broncho-pneumonia and rickets, May 25, 1910. It was thought the child did not see properly, and amaurotic idiocy was suspected. Mr. Treacher Collins made an examination of the eyes, with the following result: "Around each macula there is a circular area of white opacity on the retina. The macula itself appears as a dark red spot. The margins of the optic disks are well defined, but they are pale, especially on outer side. The case is one of so-called amblyopic idiocy met with in Jewish children" (E. T. C.)

The case was then transferred to the care of Dr. Mott. The mother, a Polish Jewess, who could speak only broken English, gave the following history: The child has been ailing for about four months with

frequent colds and a cough. A week ago the cough became worse. During the last two days the child has been drowsy and partly unconscious at intervals; she has also had twitchings in the arms, and at times gives sudden jumps. There has been no diarrhœa or vomiting, and food has been taken well.

Family history: The following history and pedigree were kindly obtained by Dr. Rees Thomas. Patient is the youngest child of a family of seven. There is no family history of asthma, consumption, epilepsy, insanity, or rheumatism. No case of blindness occurred in any of the children that died young, but the first two children (girls) both died at the age of 1 year from pneumonia, and it is possible that they were afflicted with amaurotic idiocy which, as in this case, was not detected. The third child, a boy, died at the age of 2 years from measles. The other three children, one boy aged 6, and two girls aged 4 and $2\frac{1}{2}$ years respectively, are alive and healthy.

On admission: The child lay in a semi-comatose state, slightly cyanosed, and took no interest while it was being examined; it neither cried nor struggled. Conjunctival reflex was very dull. Its hands and feet were cold. Respirations 70, pulse 170, temperature 103.4°F . Breath-sounds very harsh, and in patches bronchial in type. Moist râles, bronchi and crepitations could be heard. Abdomen lax. Head not retracted.

The physical condition of the patient improved under treatment. Its appetite never seemed to be satisfied; it was always crying, but upon giving it milk the crying would cease. It certainly heard loud noises, but exhibited no signs of disgust when medicine was given. Death occurred on July 17, 1910, and the autopsy was made by Dr. Mott.

Post-mortem notes: Physiognomy indicates no degeneration, like that of an idiot or imbecile. Palate shows no abnormality, broad and flat. Two central incisors, upper and lower, cut. Lower incisors notched, but certainly not indicative of congenital syphilis. No bruises or rashes. A little lividity of dependent parts. On opening chest and abdomen there were no adhesions or fluid. No fluid in pericardium. Slight beading of ribs. No indication of rickets in legs. Fontanelles still open. Tongue, fauces, tonsils, and larynx normal. Muscles good colour. Lungs: Some congestion of both bases. Heart apparently normal. Liver pale and mottled, suggestive of fatty change. Spleen normal. Adrenals small and pale. Kidneys rather paler than normal. Mesenteric glands: A few slightly enlarged; large gland near cæcum. Brain weighs 970 grm.: right hemisphere, 435 grm.; left hemisphere, 435 grm.;

pons, &c., 100 grm. No excess of fluid. No flattening of convolutions; decidedly firmer to touch than normal, has a leathery feel. Meninges not thickened; convolutional pattern complex. Sylvian fissure horizontal. Portions of the organs and the brain were removed for microscopical and chemical examination (*vide* pp. 188).

HISTORICAL SUMMARY.

It was in 1881 that Waren Tay, of the London Hospital, discovered this disease, and his description of the ophthalmoscopic appearances, which has now become historic, may be read in vols. i and iv of the *Transactions of the Ophthalmological Society*.¹

Under the heading, "Symmetrical changes in the region of the yellow spot in each eye of an infant," he says that in a child aged 12 months he found "the optic disks apparently quite healthy; but in the region of the yellow spot in each eye there was a conspicuous, tolerably defined, large white patch, more or less circular in outline, and showing in its centre a brownish-red, fairly circular spot, contrasting strongly with the white patch surrounding it. This central spot did not look at all like a hæmorrhage, nor as if due to pigmentation, but appeared to be a gap in the white patch through which one saw healthy structure. In fact, the appearances may most suitably be compared with those we are familiar with in cases of embolism of the central artery of the retina." In a note made five months later he adds that "the disks are undoubtedly becoming atrophic."

The disease was named "amaurotic family idiocy" by Sachs in 1887 [11]. Twenty-eight of his cases occurred in fifteen families, and extensive degeneration of the cortical pyramidal cells was described. A few years after Sachs' publication, Hirsch found the same changes, not only in the cortical grey matter, but also in the grey matter of the entire central nervous system, including the spinal ganglia; and these observations were confirmed by Sachs in 1903 [12].

Further corroboration was brought by Schaffer in a recent study of eight cases [14]. The name Tay-Sachs disease, by which it is sometimes known, was proposed by Higier, and in 1908 Apert collected 106 cases, of which seventy-three occurred in twenty-five families [2]. The observation that the disease is confined to Hebrews was made by Carter [3]. There is abundant evidence to prove that the retinal changes are not present at birth.

¹ *Trans. Ophthalm. Soc., U.K.*, 1881, i, p. 55; 1884, iv, p. 158.

In a case reported by Koller [7], a child aged 2 months showed signs of muscular weakness; but no unusual appearance was seen except an indistinct brownish patch at the foveal spot in one eye.

In 1894, Kingdon published a case of a child aged 9 months, who showed the typical ophthalmoscopic appearances [5]. He had examined this child when it was 3 months old, and when muscular weakness was commencing. The fundus was then normal. At a second examination, when the child was 5 months old, there was a suspicious haze at each macula.

Children affected with this disease as a rule succumb at about 2 years old, but cases have been recorded of children who lived for some years longer. Sachs is surely unduly careful when he says that the disease is "generally fatal" [13]. One of his cases was $5\frac{1}{2}$ years old, and Koller [7] has recorded a case of a patient who had optic neuritis at the first examination at 2 years of age, and who when nearly 4 years old could crawl about and mutter a few words. In the region of the macula there was "a slight veil-like, milky-bluish haze, gradually fading into the colour of the surrounding retina. In the centre of the opacity at the site of the fovea centralis was a cherry-red patch, not very dark, a little smaller than the disk, and with ill-defined outline."

It is well recognized that syphilis is not a factor in the disease; and hitherto no genuine case of amaurotic idiocy has been recorded in any but Jewish children. It has been asserted that the disease is restricted to Polish Jews, but this is not so; German and Polish Jews are likewise affected.

Sachs [13], in his recent paper on the disease, gives it as his opinion that the tendency to the disease is born unquestionably with the child, and that it is not acquired, nor due to a toxic cause. Afflicted children are "possessed of a nervous system so inadequate to the demands imposed upon it that its cells, after having performed their function for a few weeks or months, undergo complete disintegration."

More than one observer has recorded cases which in some degree resemble amaurotic idiocy, but which lack certain characteristic features. The family element may be absent; but it must be remembered that in but few such cases can we be sure that no more children would be born to the parents.

It has been stated above that the true disease is found only among Hebrews. Wandless [19] has recently reported, as atypical examples of amaurotic idiocy, three cases in a family known to be five-sixths Irish. One of the children was 14 years old when he died, and a second was

8 years old at the time of observation. The choroid and retina were atrophic, the latter showing pigmentation; the usual changes in the macula were not present. The autopsy showed complete optic atrophy. The retinal layers were hopelessly degenerated and no ganglion cells could be found. The ganglion cells throughout the whole nervous system were markedly degenerated, and degeneration was observed in the thymus, adrenal bodies and pituitary gland.

Parhon and Goldstein [9] record the first case observed in Roumania. The child was a Jew and was 14 months old.

Spielmeyer [17] describes a special form of the disease in which mental weakness, blindness, and a family character of the illness were present, but the former did not show itself till 6 years of age, and death did not occur until puberty.

Spiller [18] also refers to a patient whose illness was allied to amaurotic idiocy, and who lived until 8 years old.

Gordon [4] reports two cases of Russian Hebrew children, a brother and sister, in whom mental deficiency was noted in infancy, and blindness very early in life. Optic atrophy was present, and an irregular patch of absorption of choroidal pigment was observed in each eye, but there was no cherry-red spot at the fovea. He urges the opinion that anomalies in the structure and function of the ductless glands may be the real cause of the disease.

Kingdon and Russell [6], in 1897, published a paper dealing with "infantile cerebral degeneration with symmetrical changes at the macula." Five children in a family of seven were affected. In one of these cases an autopsy was made, when degeneration of the cortical pyramidal cells was found, with sclerosis of the pyramidal tracts; and a large amount of free fatty material was distributed throughout the sections. There was no evidence that these changes had occurred in other than normally developed tissues. The authors state that "so far as has been discovered the lesion is purely cortical, and it is just possible that the retinal changes are due primarily to a degeneration of the ganglion cells similar to that met with in the pyramidal cells of the cortex, and that the limited ophthalmoscopic appearance is partly due to a much greater abundance of those cells in the macula region."

Schuster [16], in a comprehensive survey of the subject, mentions five types of the disease, but he points out that, although their general similarity is remarkable, it is doubtful whether they can all be correctly included. Some stress is laid upon the fact that the disease is independent of any lesion of the blood-vessels. In the case which he reports the child died at the age of 15 months. The rods and cones were

normal in places, but swollen for the most part. In the foveal region the outer nuclear layer showed the following change—namely, the cells were placed in a convex layer as though increased in the direction of the vitreous, whilst the scleral side showed concave formation. The inner nuclear layer was much altered, many cells having perished. The outer molecular and Henle's layer were very much pronounced and less firm than usual. Schuster thinks that from the various changes seen œdema of the macula region was present. He says that no absolutely normal ganglion cells were present in the retina, and he summarizes the changes of individual cells as follows: Increase in volume; nucleus eccentric, dark and surrounded by dense protoplasm; knot-points of meshwork which fills cells thicker than normal; Nissl granules not preserved; gradual vacuolation. In some cells the diseased dendrites were clearly seen.

A few years ago Schaffer, of Budapest [15], contributed an interesting and well-illustrated article on this disease. He characterizes the minute pathology of amaurotic idiocy as a cell swelling. The details are best seen at the ampulla-shaped swellings on the dendrites; the individual fibrils are made to stand out, and their wave-like form is remarkable. Schaffer insists that it is the interfibrillary material which is first attacked, and that the cell degeneration follows. This view is supported by observers who consider that it is the interfibrillary substance or hyaloplasm of the cell and dendrites which carry the nervous impulse. Glia proliferation was well demonstrated. Bielschowsky's method showed that the optic nerve was normal, the inference being that the loss of vision was caused by a central cortical lesion.

From an examination of cells stained by Nissl's method, Schaffer concludes that the cell body is filled with two forms of network—namely, the nervous framework or inner neuro-reticulum, and a non-nervous spongioplasm (Cajal). The latter is more clear in pathological cells because in these the Nissl bodies have disappeared.

It was further observed that the structure of the cell nuclei was peculiar; the nucleus was seen to consist of threads, which possibly corresponded to chromatin, and which formed a network, which occurred in part only of the nucleus. This is not seen in normal nuclei, and Schaffer thinks it possible that disease of the cell causes a temporary greater activity of the nucleus. All parts of the cortex showed a remarkable lack of fibres. Schaffer concludes by expressing the opinion that children with amaurotic idiocy possess an abnormally exhaustible nerve-cell protoplasm, which, becoming paralyzed with the strain of the earliest functions, soon degenerates.

The characteristics of Mott's two autopsies [8] were: Absence of healthy cells in brain and cord; absence of Nissl granules in most of the Betz cells; glia proliferation; sclerosis of pyramidal tracts. No fibrils were seen coursing through the cells, as described by Gordon Holmes. In the case of the second patient (Case IA), Mott found acute inflammation of the liver and pancreas, which suggested a toxic cause for the illness. In the brain there was almost complete disappearance of tangential fibres, with marked diminution of the super-radial and inter-radial fibres. The radial fibres were abundant (Weigert-hæmatoxylin). The anterior and posterior cord roots showed fairly normal bundles of myelinated fibres, indicating that, although profound changes had occurred in the cytoplasm of the ganglion cells, the axons were still capable of function. This fact is important, taken in conjunction with the statement that it is the interfibrillary substance of the cell, and not its fibrillary conducting material, which suffers the primary, and so far invariable, change in the disease.

Mott, in 1907, thought it probable that every nerve-cell in the body was affected by the morbid process, and he concluded that "this extraordinary regressive metamorphosis is brought about by a conspiracy of morbid factors—namely, an inherent racial lack of specific neuron energy and some general alteration in the chemical composition of the blood, either by the existence in it of a neurotoxin, or by the failure of some chemical substance to form in sufficient quantity, for the building up of the nucleo-proteid substance of the nervous system."

The most important observations which have been made on the disease in England in recent years have been embodied in papers by Mott in the *Archives of Neurology*, 1907 (*vide supra*), and by Poynton, Parsons and Gordon Holmes in *Brain*, 1906 [10]. The following conclusions were arrived at by the latter authors as the result of an elaborate microscopical examination of the nervous system:—

(1) That there is strong evidence that amaurotic family idiocy is a primary disease of the nervous elements, and that the neuroglia proliferation is secondary to this degeneration.

(2) That inasmuch as the nerve-cells are relatively more affected than the fibres, and as in certain tracts there may be no visible change in the fibres, the affection may be considered a primary cell disease.

(3) That the primary change is disease of the interfibrillary protoplasm, because this is very much more severely affected than are the neurofibrils. They also conclude that: (*a*) The disease is not due to arrested development, because there is no reason why, if this were the case, such an arrest should cause a progressive and invariably fatal

disease; and because, if it were so, the symptoms would probably be evident from birth. There is also little anatomical evidence of mal-development. "The most easily obtained evidence of the completed development of the central nervous system—namely, myelination of the fibres—proves that the final development of the different parts of the brain is completed at different periods in a fairly long space of time, and is not ended until a few months after birth. But the examination of these brains does not indicate greater abnormalities in the regions which develop late than in those where development is completed early in intra-uterine life—e.g., the visual cortex, which is myelinated very early, is quite as severely affected as the prefrontal region in which the myelinated fibres appear late. If, however, the disease dates from the earlier months of extra-uterine life, the development of fibres which myelinate late may be checked, owing to deficiency of trophic influence from the diseased cells." (b) The disease is not due to bacterial toxins, but to (c) some inherent biochemical property of the protoplasm of the cells, as the result of which it undergoes certain changes which result in its degeneration."

The authors further state that, on pathological grounds, the disease is one "*sui generis*," and must be separated from the class of diplegias. In this disease the nerve-cells are reduced in number, and those which remain are shrunken and atrophic. The myelinated fibres are those most greatly affected, and, unlike amaurotic family idiocy, the disease is often associated with gross defects or macroscopical changes in the brain.

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PART II.—BY DR. MOTT.

HISTOLOGICAL AND CHEMICAL EXAMINATION OF THE
NERVOUS STRUCTURE.*Preface.*

The histological and chemical investigations contained in this communication were carried out in the Pathological Laboratory of the London County Asylums, Claybury. A portion of the microscopic investigation was made by Dr. Carlyll under my direction, and I wish here to acknowledge my indebtedness to Dr. Fortuyn for his investigation of the cell lamination in the visual and auditory areas; to Dr. Edgar Schuster for three very admirable drawings, and to my assistant, Mr. Sydney Mann, for his chemical investigation, the results of which form an appendix.—F. W. MOTT.

Introduction.

I described two cases of this disease very fully in vol. iii, *Archives of Neurology*. I mentioned there my reasons for terming the disease amaurotic dementia rather than amaurotic idiocy. I pointed out that the brains were of normal size or even larger than normal average; moreover, the convolutional pattern was in no respect like that of an idiot's or imbecile's brain; in these two cases the Sylvian fissure did not slope obliquely upwards and backwards as in the simian brain, and the superficial surface of grey matter, owing to the complexity of the convolutions, was by no means deficient in extent; neither did the microscopic examination of the cortex cerebri indicate a deficiency in numbers of the cortical cells. Moreover, I showed that the same characteristic change which is known to affect the cerebro-spinal ganglion cells also affected the sympathetic.

I have since had the opportunity of examining four such brains of children dying of this disease, three of which were from Cases I, III and VII. In all these cases the brains were of normal average weight, and the convolutional pattern complex, and in no way denoting either imbecility or idiocy. Again, I have had the opportunity of examining the central nervous system in all these cases, and I do not find a deficiency of numbers of the cortical cells. Moreover, the sympathetic ganglion cells I found showing the same change, only not

so advanced as the cerebrospinal ganglion cells. It may, therefore, be concluded that the disease is an affection of the whole of the neurones of the body. It cannot be present long before birth or the convolitional pattern would not develop to its perfect form. We have to ask ourselves, therefore, what is the cause of this extraordinary disease, in which the microscopic morphological changes in the nervous system, and the clinical phenomena are so characteristic as to be unmistakeable for any other disease? Is it an acquired disease? If so, what conditions of life should limit this disease to the Jewish race. So far, I have been unable to associate it with any condition of food or environment; it appears to occur in both breast-fed and artificially-fed children, and I am inclined to agree with Sachs that there is little evidence to show that conditions of food or environment can account for the disease. Since it affects only the offspring of Jewish parents, and frequently several of the offspring of the same parents suffer with this disease and die of it, it follows that racial and family heredity do play a part, and probably are solely responsible for its occurrence.

MORPHOLOGICAL AND CHEMICAL INVESTIGATIONS IN RELATION TO THE PATHOGENESIS.

The evidence I have adduced shows that all the nervous units are present at birth, but from some cause or other their specific vital energy is so deficient that they are unable to maintain physiological equilibrium; they are unable to store any reserve of the Nissl substance which many authorities regard as the material basis of nervous energy; in consequence of this, and probably also from the swelling of the cell, the conductile mechanism itself (neurofibrils) undergoes destruction, with morphological and bio-chemical changes in the neurones. As the neurones degenerate and die the neuroglial cells proportionally proliferate and increase in size, thus altering the consistency and feel of the brain itself, which has a tough, leathery character. Do the neurones die because of an inborn deficiency of specific vital energy, or do they die because the ambient medium contains some toxic substance or lysin which destroys them, or is it because the ambient medium is lacking in some substance necessary for the development and maturation of the neurones? If it were a toxin or lysin we should rather expect it would act equally on all the cells of the body, and certainly all the nerve-cells, which is not the case. It might be a deficiency in the blood of some substance, for we know that cretinism is due to an absence of the

thyroid gland; but cretinism is a condition of obvious defective brain development—in fact, we have an idiot's brain. The thyroid is not affected in Tay-Sachs disease, nor can I find any gland which is affected; and I have examined all the tissues of the body in several cases. We now come to the only other cause—viz., an inborn lack of specific vital energy of the nerve-cells, due to a racial inherited failure of the germinal determinants of the nervous system.

The neurones are perpetual elements, they are all present at birth with all their innate potentialities to respond to stimuli from without; this leads to their acquiring connexions and associations with one another; in no part of the body, excepting the reproductive organs in adolescence, do such important synthetic chemical changes take place as in the central nervous system of the human being in infancy. The Nissl substance has to be accumulated in the nerve-cells, especially in those of later phylogenetic and ontogenetic development; the myelin has to be deposited around the axial fibres of the neurones, particularly in the brain cortex, where there is scarcely any present at birth. How is this accomplished? Although stimulus from without by all the sensory avenues plays some part in accelerating this synthetic process, nevertheless every neurone has a specific autonomic inherited energy apart from stimulus. The experiments of Ross Harrison demonstrate the truth of this fact. The principles of heredity tell us that this autonomic specific energy resides in the nucleus, which is the soul of the neurone; and the experiments of Loeb upon parthenogenesis in Sea Urchin eggs show that the nucleus possesses an auto-katalytic ferment, which in the process of segmentation of the egg-cell in reproduction is capable of decomposing the lipoids of the cytoplasm and recomposing from the products a more highly phosphorized substance, nuclein.

The experiments of Verworn and others tend to show that the Nissl substance is a store of reserve neural energy, and it is contained in the meshwork of the conductile neurofibrillary substance; the observations of Macallum showed that it is a nucleo-protein containing phosphorus, and it is not unreasonable to suppose that the nucleus of the neurone produces a ferment substance which, passing into the cytoplasm, elaborates the Nissl substance out of a phosphorized lipoid obtained from the ambient medium; this basophil chromophilous material contained in the interfibrillary meshwork forming a pattern according to the arrangements of the fibrils. Verworn and his pupils' experiments indicate that this substance unites with oxygen and forms a store of neural energy. Marinesco terms it kinetoplasm.

Now, if we study the microscopic morphological characters of this disease we shall note a very remarkable and characteristic disappearance of the Nissl granules, so far as I am aware, not observable in any experimental conditions, such as ligature of blood-vessels, hyperpyrexia, or toxic conditions in mammals. Nor have I seen such change in any human pathological condition. Generally, when the cell is swollen the nucleus becomes eccentric and the Nissl granules are only found at the periphery of the cell; the chromatolysis is perinuclear, just the converse of what is found in this disease. In alcoholic and lead neuritis the anterior horn cells and the Betz cells of the cortex show perinuclear chromatolysis, which is doubtless due to reaction of injury to the axon combined with toxic conditions of the blood.

In Tay-Sachs disease, as is well known, the Nissl substance disappears from without inwards towards the nucleus, and as the Nissl substance vanishes so the cell swells up as if a process of hydrolysis had taken place. In the later stages no Nissl substance can be seen upon the dendrons, which are also swollen irregularly; no Nissl substance can be seen in the greater part of the cell body, which has undergone a bladder-like distension and often curiously and characteristically distorted into an hour-glass shape. The swelling and distortion of the cell is generally proportional to the disappearance of the Nissl substance, and finally there is only a halo of deeply stained basophil substance around the nucleus, which may now be displaced from the centre of the cell; in the case of the pyramidal cells of the cortex it nearly always takes up a position at the base of the apical dendron (*vide* fig. 13 (1)). If the sections are stained with toluidin blue or polychrome blue it will be found that the bladder-like swollen cells show a fine intracellular network which stains at the nodal points (figs. 13 (4) (5)); the network stains owing to a film of incrustation of basophil chromophilous substance. Later, when the change is more intense, the network is incomplete and unstainable areas are seen. I have, so far, only dealt with the cells stained by basic aniline dyes, but we shall not have a true picture of this disease unless many methods of staining are adopted—methods which are applicable to the demonstration of particular structures.

I shall now advance proofs that the process of decay and death of the neurones is characterized by a fatty degenerative change with destruction of the intracellular neurofibrils; there are also changes occurring in the staining reaction of the nucleus, and eventually the nucleus itself is destroyed, although that is a comparatively infrequent event.

CELLULAR CHANGES.

The nuclear membrane is sometimes stained with basophil dyes deeply; also the nucleolar and intranuclear network. Generally in cells which show a marked degree of swelling, the nucleoplasm also stains with the basic dye. In the normal cell the nucleoplasm is unstained by basic dyes. This microchemical basophil reaction suggests a change in the normal biochemical function of the nucleus. Are these cell changes due to a failure in the ambient medium of the necessary materials which may be required by the nuclear ferment to form the nucleoprotein Nissl substance, or is it some progressive failure of the nucleus in its reaction on the cytoplasm, causing the cell to swell up and eventually break up and destroy the intracellular network? The dendrons also show characteristic swellings (*vide* fig. 13 (8) (9), and fig. 15). Although all the nerve-cells of the central nervous system show the fatty change in some degree, including the ganglion cells of the retina, which, as we know, are developed by a bud from the forebrain, yet the neurones are not equally affected in the whole nervous system, nor even in sections of the same part; therefore, specific cell energy does play a part, whichever view is taken, regarding the pathogenesis. The chemical analysis of the brain as compared with a normal child's brain of the same age shows a deficiency in organic phosphorus and sulphur, and an increase of water-soluble extractives, containing phosphorus and sulphur. Consequently we cannot suppose that there is an increase of lipoids in the cells, due to accumulation; but it rather shows that the nucleus provides a splitting ferment, whereby the cell-plasm is decomposed and broken up, but the nuclear activity does not complete the vital process by a synthetic action; thus there may be a chemical decomposition on the way to a fatty acid, e.g., choline, glycerophosphoric acid and stearic acid, and no recombination. A fatty acid or soap, or some lipid, which takes the Scharlach stain in various degrees of intensity, may account for this reaction. The cells are also stained by the Marchi-Pal and Heidenhain methods in varying degrees of intensity; in all cases taking the form of very minute particles, which is additional evidence of its fatty degeneration. In the cortex of the cerebrum and in the cerebellum, where the degeneration is most intense, an immense number of granule cells (Körnchenzellen) are seen; these contain larger ruby red granules, and are seen scattered throughout the whole of the cortical grey matter of both the cerebrum and the cerebellum. At first I

thought these were ganglion cells, but when Scharlach-stained specimens are counter-stained with methyl violet, with methyl blue, or logwood, it is then seen that these cells have a nucleus in the middle, and that several together lie on a ganglion cell, and almost, or completely, obscure it; sometimes two of these granule cells, joined together, occupy the position of a degenerated ganglion cell, and take on the characteristic hour-glass appearance. It may generally be said that the nerve-cells very seldom indeed show any coarse granules. It looks as if the neuroglia cells possessed a phagocytic function, as was first pointed out by Bevan Lewis, and I have seen in both silver preparations and preparations stained by other methods (photomicrograph 5) appearances suggesting phagocytic activity of the neuroglia cells.

Two of the three brains examined showed numbers of granule cells in the white matter as well as the grey, this showing that these cannot therefore be ganglion cells which have undergone this degeneration. Numbers of cells filled with deep red stained fat granules are also to be seen in the perivascular lymph sheaths, as if the endothelial cells or cells of the adventitia had taken up the fatty matter. Curiously enough, not much change was found in the cerebrospinal fluid withdrawn during life by lumbar puncture.

All the facts show that in this disease there is a fatty degeneration of the cytoplasm of the neurones, which I find Alzheimer describes in a recent publication. The satellite cells found in the perineuronal spaces, or neuroglia cells, show a fatty change, which is probably of the nature of an infiltration; that is to say, these cells have devoured the fat produced by the degeneration of the neurones; the fatty contents of these cells indicate a further process of change, judging from the deeper coloration by the Scharlach dye, and the larger size of the globules (*vide* Plate I). The appearance of the nerve-cells of the cortex makes it possible that the late stages of hydrolysis convert the cytoplasm into a thick emulsion, giving the cell that peculiar appearance which is not unlike that of the cortical cells of the suprarenal body, which we know contains a phosphorized fatty substance that stains deeply with Scharlach R. Moreover, I have noticed that when there is a considerable amount of glia fibrillation of the superficial layers of the cortex, and the microscopic examination of sections of the cortex shows a marked condition of fatty change in the cells (*vide* photomicrograph 8), that the brain substance is semifluid, like cream, so that the tough, leathery, fibrillated superficial layer of the cortex can be peeled off from the subjacent semifluid, creamy grey matter.

DETAILED DESCRIPTION OF FIGURES AND PHOTOMICROGRAPHS.

I will now describe, with the aid of the accompanying figures and photomicrographs, the cell changes which occur when sections have been stained by particular methods.

Fig. 13, a number of cells showing morphological changes.

(1) A large pyramidal cell of the cortex from a Scharlach-stained section counterstained with hæmatoxylin; the whole cytoplasm is stained an orange-pink; it presents a fine granular appearance. The cell is swollen, the nucleus is pushed up towards the base of the apical dendron, and from the base of the cell there is an oval, bladder-like swelling. (Magnification 500.)

(2) A similar pyramidal cell stained with Weigert-Pal; the cytoplasm is filled with minute blue-stained globules. The cortex stained by Marchi method would show similar globules stained blackish-grey. Again, Heidenhain's hæmatoxylin stains these fine globules blue. These fine granules thus stained may be protoplasmic particles covered with a film of fat or soap; they are the same as the fine granules seen in (1). (Magnification 500.)

(3) A cell stained by Scharlach R or Sudan III, showing much larger granules stained deep red. Most of these, and they are very abundant in the cortex, are Alzheimer's Körnchenzellen, and are either neuroglia cells or satellite cells filled with fatty droplets. It is very difficult to say whether any of the ganglion cells ever present such an appearance. (Magnification 500.)

(4) A large cortical pyramidal cell stained with toluidin blue as recommended by Schaffer, to demonstrate the intracellular network; it also shows the swelling and characteristic almost hour-glass distortion; the Nissl substance has almost entirely disappeared; there is still a little incrustation of the nodal points of the intracellular network around the nucleus. (Magnification 500.)

(5) A large spinal anterior horn cell; the same description applies as above in 4. (Magnification 500.)

(6, 7, 8, 9) Various pyramidal cells of the cortex stained by Cajal's neurofibril method. Sections were also stained by Bielschowsky's method, but the results as regards the points to be described are the same. (6) shows the basal neurofibril process split, the fibrils passing down each side of a pale substance which appears to consist of globules or round particles; the nucleus is connected with fibres coming in from the apical dendron. In (7) an appearance which is very rarely seen is

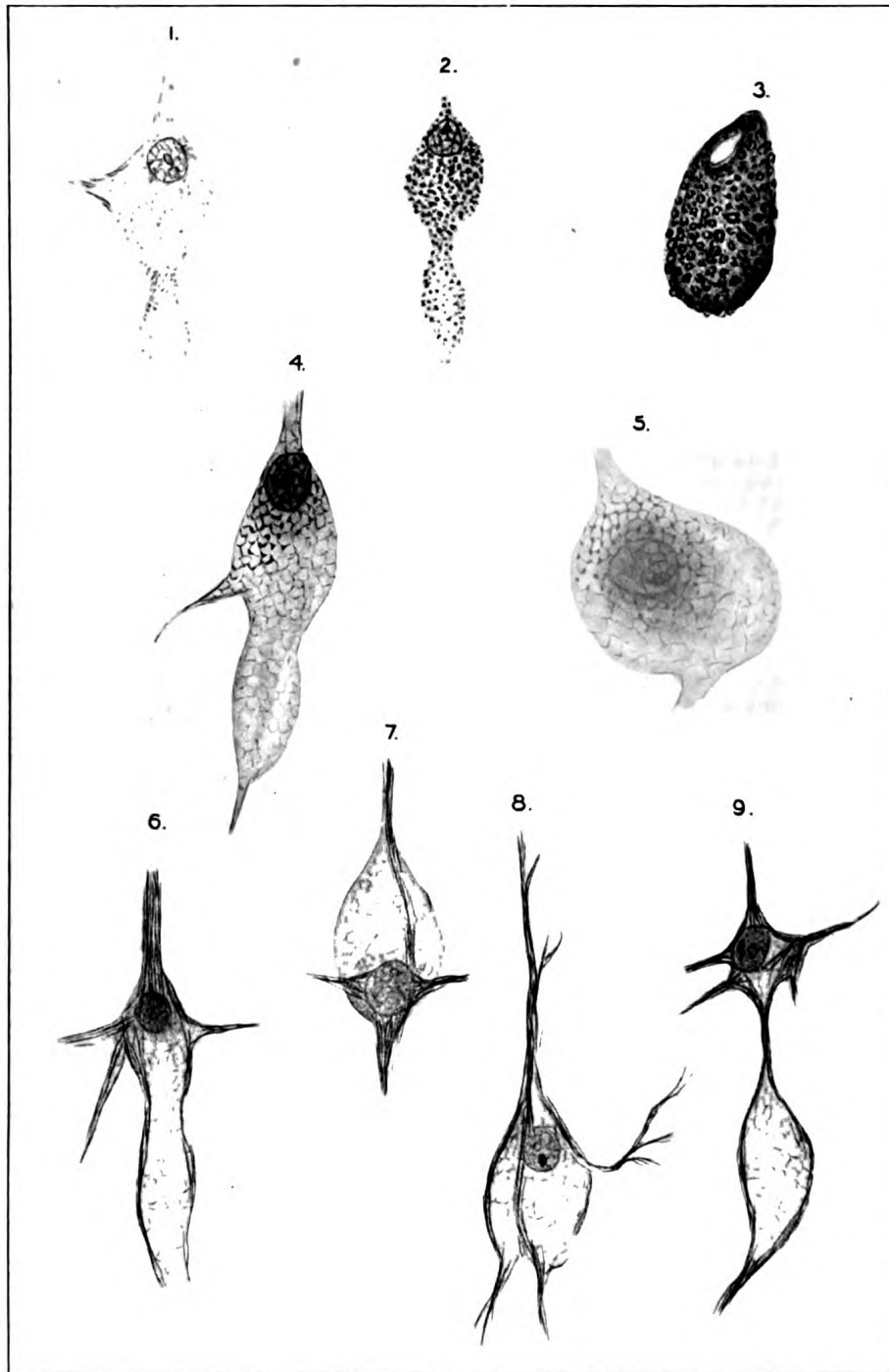
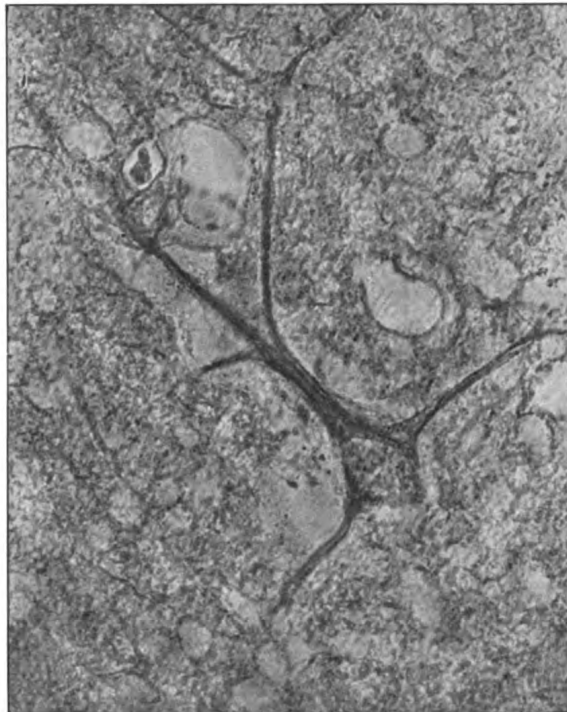


FIG. 13.

shown ; here the nucleus is apparently held in position by intact neurofibrils passing across the cell from one lateral dendron to the other. (8) shows an appearance not infrequently seen of the fibrils of the apical dendron passing along the periphery of the cell to other processes. (9) shows a large ovoid swelling on one of the processes of a ganglion cell as if the hydrolytic process had commenced in the process instead of the body of the cell. (Magnification 400.)

Photomicrograph 1.—A nearly normal cortical pyramidal cell showing abundant neurofibrils in the processes ; this was the only one seen in a section showing hundreds of cells in a state of degenerative decay. (Magnification 1,080.)

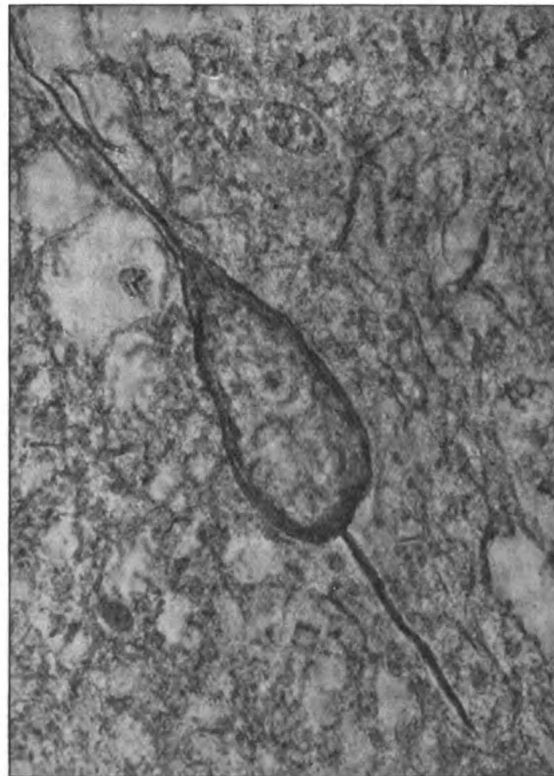


PHOTOMICROGRAPH 1.

Photomicrograph 2.—A pyramidal cell in which the only fibrils are seen at the periphery and in the two processes. The fibrils seem to be continuous between the apical dendrons and the axon. The whole central portion of the cytoplasm has a coagulated structureless appearance. (Magnification 1,180.)

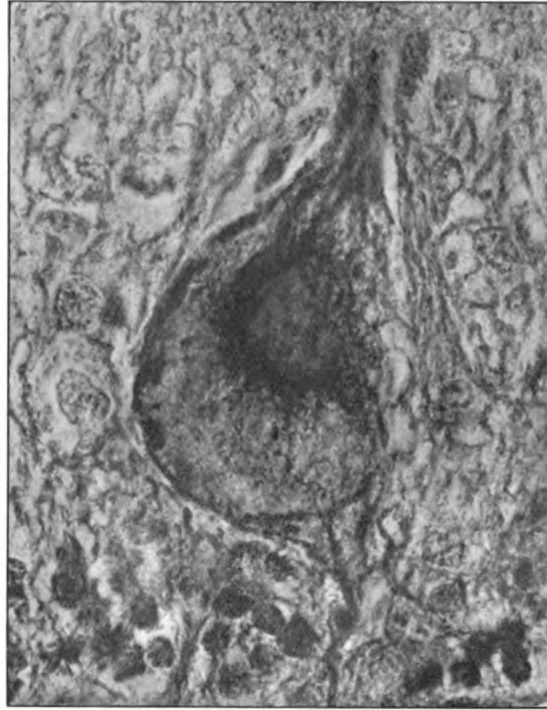
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Photomicrograph 3.—A cell of Purkinje stained by the neurofibril method. The fibrils can be seen passing from the apical dendron to the nucleus and around the periphery of the cell continuous with the fibrils of what appears to be the axon, arising from the lower portion of the distorted, flask-shaped cell. It will be observed that all around the nucleus there is a complete absence of fibrils. I attribute this to the disappearance of the basket-like terminal arborization of the stellate cells, which a subsequent illustration will show are degenerated earlier than the Purkinje cells. (Magnification 1,260.)

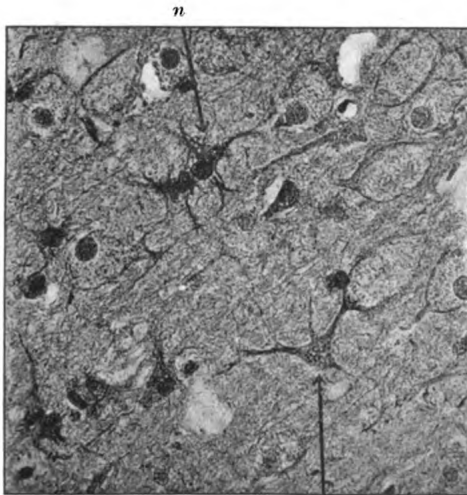


PHOTOMICROGRAPH 2.

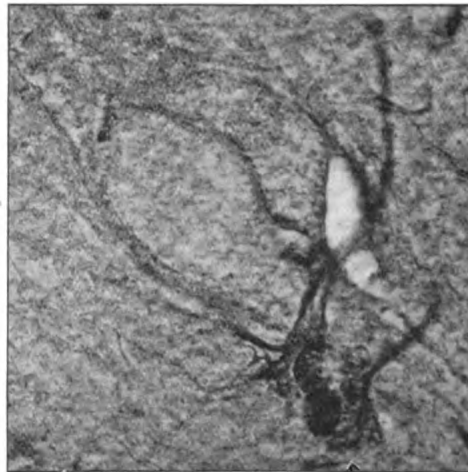
Photomicrograph 4.—Cortex stained by neurofibril method. Numbers of bladder-like cells are seen with a fine granular central portion and externally surrounded by dark-stained fibrils; *g* shows a ganglion cell which apparently is intact as regards its neurofibrils except that one process appears to be surrounding a degenerated cell. It will be observed that this nerve-cell differs markedly from the black-stained



PHOTOMICROGRAPH 3.



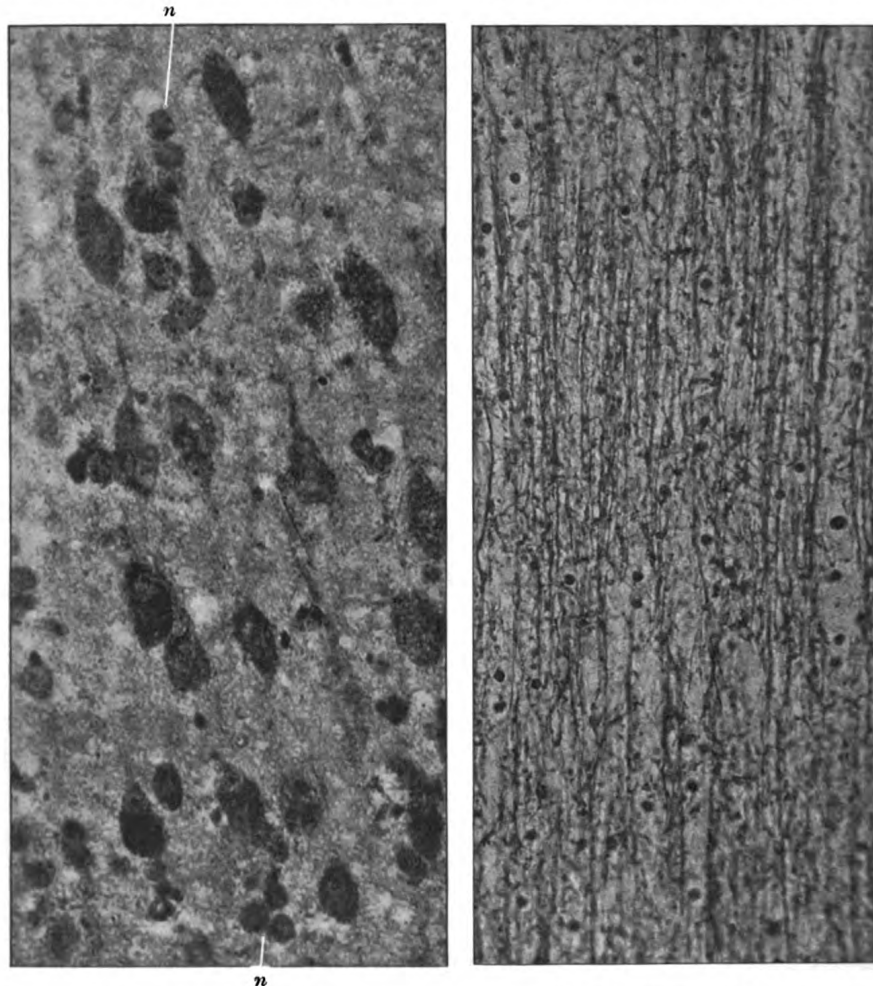
PHOTOMICROGRAPH 4. ($\times 360$.)



PHOTOMICROGRAPH 5. ($\times 810$.)

neuroglia cells *n*, of which there are great numbers undergoing proliferation. (Magnification 360.)

Photomicrograph 5.—A large neuroglia cell, showing two nuclei and large stout processes, apparently stuck on to and grasping with its processes a large degenerated ganglion cell, but some of the fibrils which seem to come from the glia cell can, by close observation, be seen



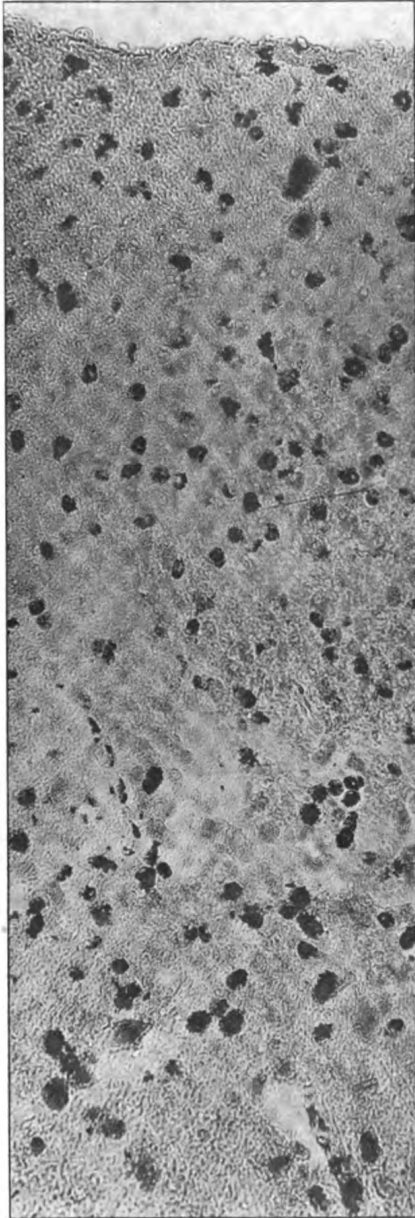
PHOTOMICROGRAPH 6.

PHOTOMICROGRAPH 7.

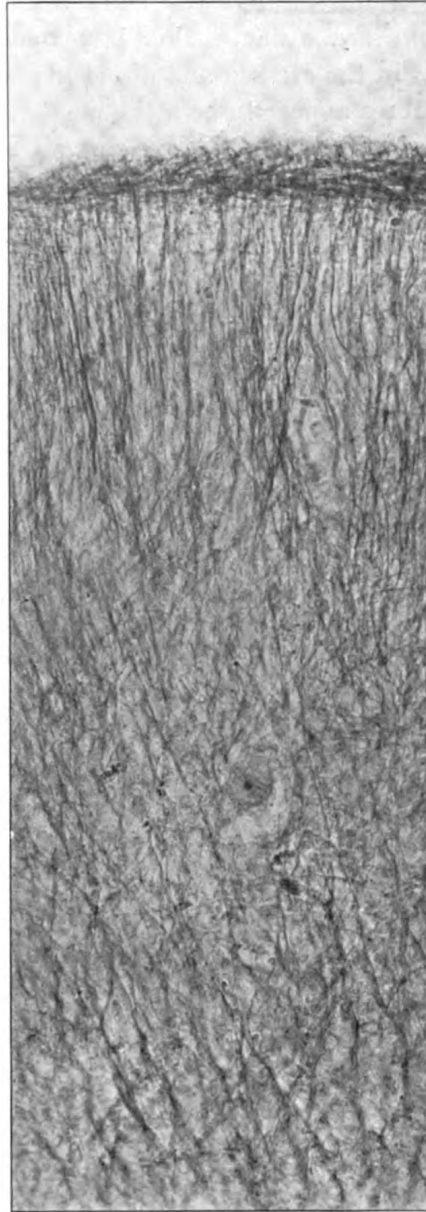
to be the undestroyed peripheral neurofibrils of the ganglion cell. (Magnification 810.)

Photomicrograph 6.—Cortex stained by Weigert (neuroglia method), subsequently by iron hæmatoxylin (Heidenhain's method). The swollen, distorted, bladder-shaped pyramidal cells are stained purple owing to

the fine fatty globules. The nucleus is not stained deeply and it can be seen pushed up to the apical dendron. At the bottom of the picture and at the top can be seen three cells in groups *n*, round in form; these are Körnchenzellen, or granule cells, and with Scharlach or acid fuchsin are stained deep red. In the middle of the picture several can



PHOTOMICROGRAPH 8.

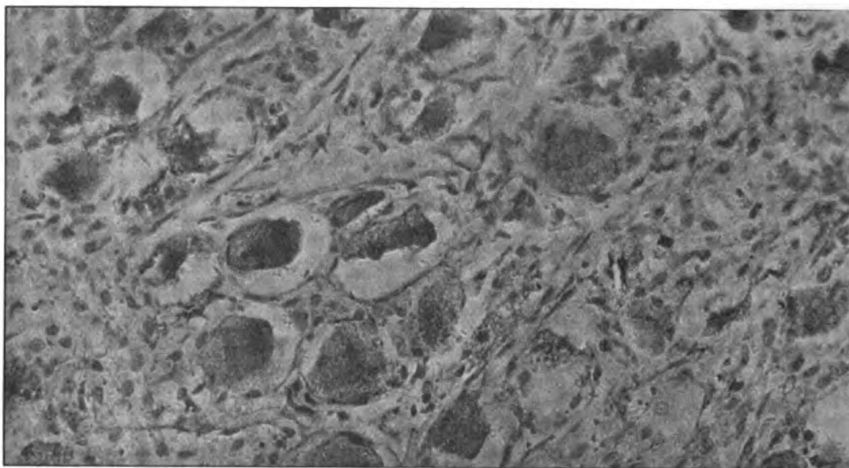


PHOTOMICROGRAPH 9.

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be seen sticking on the degenerated ganglion cells. No axis cylinder processes can be seen. (Magnification 380.)

Photomicrograph 7.—A Weigert-Pal-stained section of the subcortical white matter of the ascending frontal convolution; it will be observed that there are no coarse fibres characteristic of this cortical area present. This indicates that the large coarse fibres which form the pyramidal system are absent; this fact may be correlated with an absence of fibres in the crossed and direct pyramidal tracts of the spinal cord. All the fibres appear to be attenuated and most of them show degenerative varicosities. These fibres are all radial fibres and it will be observed that there is a complete absence of inter-radial association fibres. (Magnification 330.)



PHOTOMICROGRAPH 10.

Photomicrograph 8.—Section of the cortex stained by Scharlach R. The deeply stained cells are Körnchenzellen, the fainter stained cells with fine granules are the ganglion cells (*vide* also Plate I). (Magnification 180.)

Photomicrograph 9.—Section of the cerebellum stained by Ranke's Victoria blue method. Enormous increase of Bergmann's neuroglia fibrils is seen and a dense felting of the surface. (Magnification 450.)

Photomicrograph 10.—Section of the sympathetic (inferior cervical) ganglion showing peripheral chromatolysis of many of the cells; the change in the sympathetic ganglion is not so advanced in this case as in others that I have examined.

Fig. 14.—Section of cortex stained by Weigert-Pal method showing the terminal arborization of degenerated fibrils around cells, the bodies

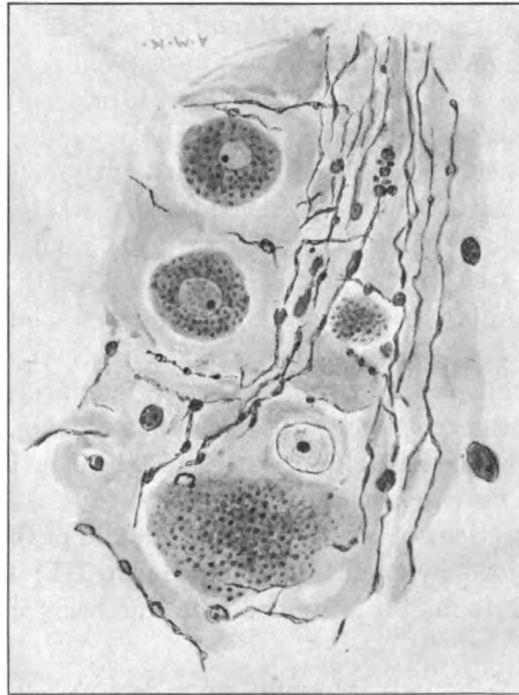


FIG. 14.

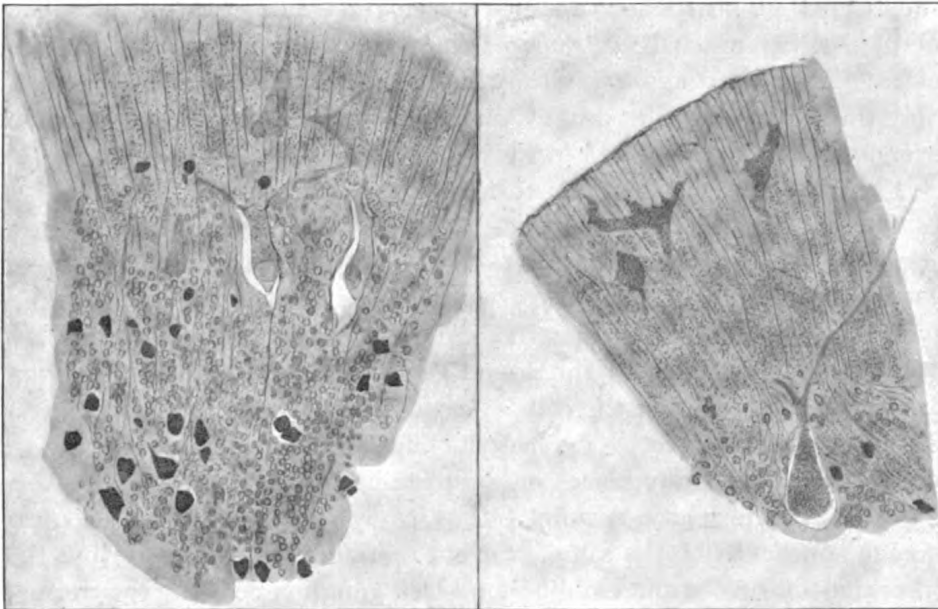


FIG. 15.

FIG. 16.

of which show minute globules stained by the dye in the same manner as the degenerated nerve fibrils. (Magnification 800.)

Fig. 15.—Frozen section of cerebellum, after hardening in formalin a few days, stained with Scharlach. A number of deeply stained smaller cells are seen amidst the granules which are unstained, many of them doubtless are Körnchenzellen; some are apparently degenerated stellate cells—viz., the cells, the axon of which form a basket-work around the Purkinje cells; the degeneration of these cells would account for the absence of fibrils seen in the greater part of the body of the Purkinje cells (photomicrograph 3). The Purkinje cells are visible because stained a pinkish orange, and the dendrons are swollen and similarly stained owing to fine granules of fatty substances. (Magnification 200.)

Fig. 16.—Another portion of the same section as fig. 15, but showing more distinctly the fine particles of fatty substance in fragments of the swollen dendrons near the surface.

As a control sections of brain of a normal child of the same age were prepared and stained by Scharlach R and Sudan III; the cells are not visible, but the white matter is stained more intensely a deep orange red.

EXAMINATION OF THE RETINA.

Portions of the retina were removed from one eye, Case VII (*vide* p. 165), and preserved for a few days in 10 per cent. formol solution. They were then floated into distilled water, and transferred to an alcoholic solution of Scharlach R, or Sudan III, in which they were left for some hours. They were again carefully floated into weak alcohol to wash away the excess of stain, caught on a cover-glass with the ganglionic layer upwards, and mounted in Farrant's solution.

Fig. 17.—Drawing by Schuster. (Magnification 240.)

The ganglion cells in the retina can be distinctly seen, owing to their deeper staining. They appear to be much more numerous in some places than others. They vary considerably in size, as the drawing (fig. 17) shows. As this method shows the whole cell it must be either assumed that as in the spinal ganglion there are cells of varying size in the retina or that the cells differ in size owing to the pathological change. Against this is the fact they are all uniformly stained a deep orange colour, in many places on an unstained background. Moreover, under an apochromatic 2 mm. 140, 4 comp. ocular, the pathological change appears to be the same. I am therefore led to believe that the difference in size is due to different-sized ganglion cells in the retina, a fact which sections would not show.

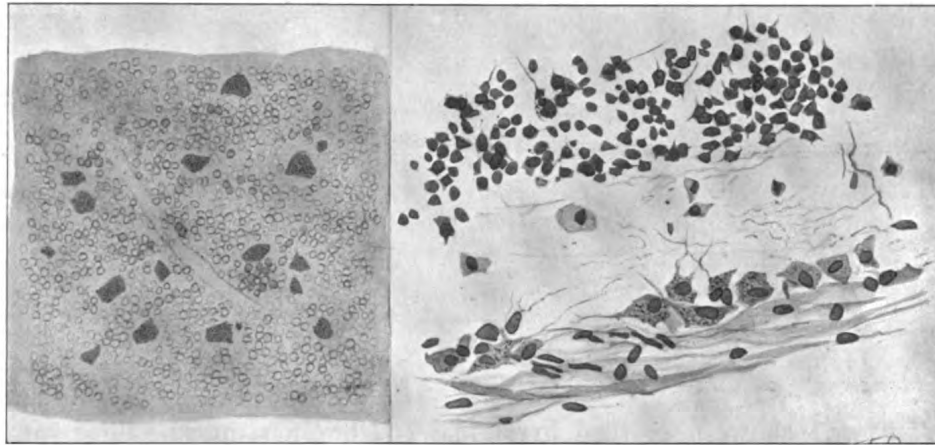


FIG. 17.

FIG. 18.

Fig. 18.—Stratum opticum. Ganglionic layer, inner molecular and inner layer of granules. (Magnification 450. Schuster.)

The other eye, after hardening in 10 per cent. formol, was embedded in celloidin, and sections through the whole eye were cut and stained by polychrome blue, Nissl, Giemsa, and Van Gieson methods. The only definite observable changes were in the ganglion layer. The cells appear abnormal in shape, the processes are either indistinctly seen or obscure. The cells lie in confused clumps, in places appearing as if joined together. The nuclei and nucleoli are well stained, but the cytoplasm is poorly stained, and appears to consist of a fine intracellular network faintly incrustated with basophil substance. No Nissl granules are seen. Here and there ganglion cells can be seen with a swollen process.

The observations of Dr. Fortuyn show that the whole cortex is similarly affected.

DESCRIPTION OF THE COLOURED PLATES.

The coloured Plates I and II are reproductions of drawings by Miss Kelley to show the appearances presented by Scharlach-stained specimens. It will be observed that the ganglion cells, wherever they are taken from, are stained a reddish-orange or orange colour. The granule cells are stained a deeper ruby-red. I may add that I have employed some of the methods of staining recommended by Lorrain Smith,¹ but I have not found that they yielded such good differentiating results as the Scharlach and Sudan III, or the fuchsin method of Alzheimer.

¹ Since this paper was completed I have received an important communication explaining the action of these various dyes on fats and lipoids: J. Lorrain Smith and W. Mair, "Fats and Lipoids in relation to Methods of Staining," *Skand. Arch. f. Physiol.*, Leipz., 1911, xxv, p. 247.

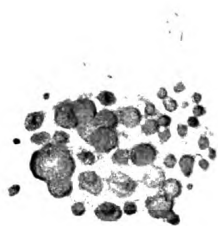
Explanation of Plate I.

Fig. 1 shows a cortical pyramidal cell swollen up, and filled with large red-stained fat globules of uneven size, and some coalescing. At the upper part of the cell is a pale unstained portion, which is apparently the nucleus. I found only very rarely ganglion cells showing this appearance. The vast majority of cells with red-stained large globules were the so-called granule cells (Körnchenzellen).

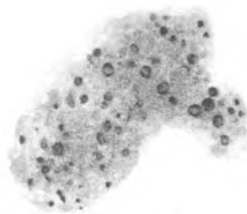
Fig. 2.—This is a distorted pyramidal cell, in which there are scattered small red globules. These, again, are rarely met with, and, as I have previously explained, many cells look like ganglion cells when only stained with the Scharlach, but which when counterstained by logwood or methyl violet prove to be one or several granule cells lying on the decayed ganglion cell, and I would not deny the possibility of this being the case in respect to both this (fig. 2) and that of fig. 1.

Fig. 3.—This is a ganglion cell in an advanced stage of fatty degeneration. The whole cytoplasm is permeated with fine globules of fat. (Magnification 600.)

Fig. 4.—A group of small cells of anterior cornu of spinal cord, stained by Scharlach. The cells are stained a pinkish-orange colour. One or two show a very fine granulation appearance. (Magnification 600.)



1



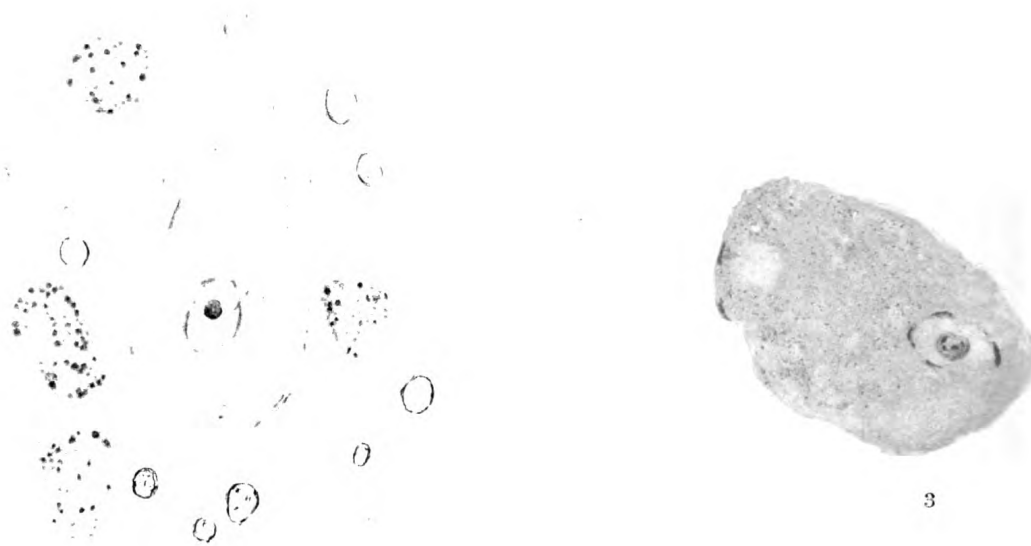
2



3



4



2

3



1

Explanation of Plate II.

Fig 1.—Section of cerebellum stained by Scharlach R. The cells of Purkinje are seen stained a light orange-red ; also a number of much smaller cells are similarly stained. But besides these paler-stained cells, which are degenerated ganglion cells (stellate cells, second type of Golgi), there are scattered about a number of deep ruby-red cells arranged in groups and sometimes in rows. These are granulation cells—amœboid neuroglia cells filled with fat globules. This particular preparation from Case VII does not show any of these granule cells in the white matter ; but in the other two cases which I have examined, numbers of these deeply stained granulation cells (Körnchenzellen) exist in the white matter ; especially are they found in numbers in the perivascular sheaths. The small granules (nerve-cells) which form such a prominent histological feature of the cerebellum did not take the Scharlach stain. (Magnification 50.)

Fig. 2.—A Purkinje cell in an early stage of degeneration. It is covered all over with very fine pinkish-orange granules. In the immediate neighbourhood are four cells containing coarse red globules. I believe they are ganglion cells, but they may be granulation cells (Körnchenzellen) in an early stage of fatty change.

Fig. 3.—A Purkinje cell showing a rather more advanced stage of fatty change ; it is more deeply stained red. (Magnification 600.)

It will be observed that the ganglion cells vary in depth of coloration by the Scharlach dye, and the deeper the colour the more obvious do the particles of fatty substance become. There is also a parallelism between the distortion in shape of the ganglion cell and the evidences of the fatty change. The fact that all the ganglion cells, with the exception of the granules, are degenerated in the cerebellum may account for the apparent absence of the basket of fibrils around the base of the cells of Purkinje; this absence of fibrils is shown in photomicrograph 3. If sections are placed first in alcohol, then in ether for a short time, the cells no longer stain, all the fat having been dissolved out.

Dr. Carlyll, in his historical summary, has given a résumé of previous observations on the morphology of this disease, but it is necessary for me to refer to some important observations by Alzheimer concerning the fatty change in ganglion cells in this disease, and in the amaurotic idiocy described by Spielmeyer and Vogt. These observations I had no knowledge of when I wrote this paper, but I have since found a description very similar to the above in Alzheimer's¹ valuable work, which he kindly sent me. He also gives a number of valuable methods of staining which I shall adopt in the study of a case that has recently died, under the care of Dr. Hume, of Newcastle, who has forwarded me the brain and the eye for examination. This will form the subject of a joint paper on the histology by the most recent methods.

CONCLUSIONS.

(1) Reasons are given why the term "idiocy" should be abandoned; it will be better to adopt the name "Tay-Sachs disease" until the pathogenesis is known.

(2) Reasons are stated why it is probably a failure in the germinal determinants of the nervous system peculiar to the Jewish race.

(3) The morphological and chemical investigations in relation to the pathogenesis are discussed, also the hypothesis is put forward that it may be due to a failure in the nuclear material of the neurones to build up the nucleo-protein Nissl substance out of lipoid substances contained in the cytoplasm, which first have to be decomposed by a nuclear ferment. The autokatalytic ferment action of the nuclear

¹ "Beiträge zur Kenntnis der pathologischen Neuroglia und ihrer Beziehungen zu den Abbauvorgängen im Nervengewebe." Nissl und Alzheimer, "Histologische und Histopathologische Arbeiten über die Grosshirnrinde," Jena, 1910, iii, pp. 401-554.

material of the fertilized ovum described by Loeb is considered as affording a somewhat analogous chemical process.

(4) Evidence to show that there is a progressive failure of Nissl substance proceeding from without inwards towards the nucleus and a corresponding accumulation of a fatty substance of the nature of a lipid, which, accompanied by a process of hydrolysis, would cause a swelling of the cell and destruction of the intracellular neurofibrillary network.

(5) The chemical analysis does not throw much light upon the question; the diminution of the lipid forms of phosphorus and sulphur is probably due to the diminution of myelin, owing to failure of development of the myelinated fibres. The corresponding increase of extractive forms of phosphorus and sulphur may be possibly due to a breaking down of the more complex to simpler forms of lipoids.

(6) The morphological changes are quite characteristic of the disease. All the ganglion cells stain with Scharlach in varying degrees of intensity, more or less intense in proportion to the degree of swelling and obvious morphological change; they also stain with Marchi, Weigert-Pal, Heidenhain—in fact, all the methods which stain the myelin sheath or fat. They do not, however, stain satisfactorily by Marchi, like degenerated myelin does when the process of decomposition has been complete to choline, glycerophosphoric and oleic acid. Consequently it is more correct to say that the cytoplasm *may be on the way* to this complete decomposition.

(7) Whereas the ganglion cells very rarely show *coarse* ruby-red globules of stained fatty substances, there are, especially in advanced cases, immense numbers of cells containing these coarse globules, and forming what Alzheimer terms *Körnchenzellen*; they are neuroglia cells which have taken up the fat from the dead and decayed ganglion cells, to which they may be seen sticking sometimes in little, closely aggregated groups indicative of active proliferation. It is probable that they have the power of decomposing this lipid of the dead ganglion cells and possibly of recomposing nuclear substance necessary for their proliferation out of it.

(8) Other methods of staining—e.g., toluidin blue, Cajal silver, or Bielschowsky—show that the intracellular fibrils are ruptured and destroyed by the swelling leaving only the peripheral neurofibrils, which can be followed from the dendrons in their course around the swollen cell to other dendrons or to the axon. In the cortex, the fibrils of the apical dendrons are seen proceeding to the nucleus, which is usually

forced up into the apex of the pyramid. It is possible that the cytoplasm is of the nature of a thick emulsion, each particle consisting of a plasm covered with a film of fat or soap.

(9) The cells of the retina, when this structure is stained with Scharlach, show a similar change to the nerve-cells of the central nervous system ; the cells are of varied size, apparently.

(10) In two of the three brains examined there was an accumulation of granulation cells (Körnchenzellen) along the course of the blood-vessels, also endothelial and connective tissue cells of the perivascular sheath could often be seen filled with the dark, red-stained fat globules.

(11) Any of the methods employed for demonstrating neuroglia shows an enormous overgrowth of fibrils, especially in the superficial layers, where it forms a dense feltwork both in the cerebrum and the cerebellum. This overgrowth is proportional to the duration of the disease. Throughout the grey and white matter the proliferated neuroglia cells of large size, with coarse and branching fibres, are seen in great abundance embracing and sticking to the ganglion cells, out of which they appear to be absorbing the phosphorized substances necessary for nuclear proliferation.

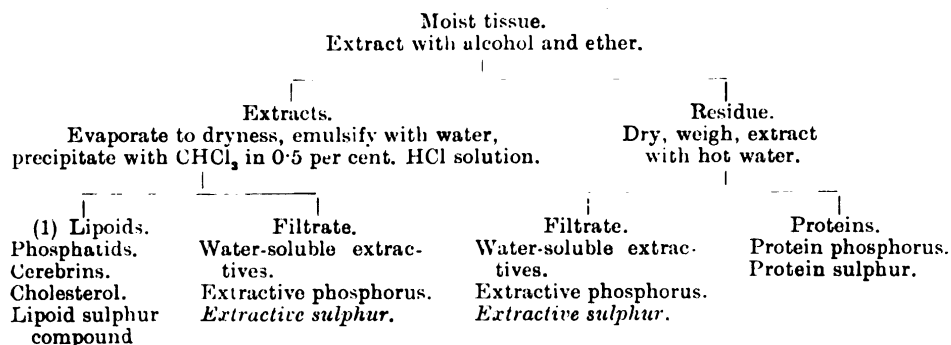
APPENDIX.

THE CHEMICAL EXAMINATION OF THE BRAIN IN TWO CASES OF
AMAUROTIC IDIOCY, AND COMPARISON WITH THE NORMAL BRAIN.

By SYDNEY A. MANN.

IN a previous investigation¹ of the brain in two cases of this disease it was shown that in the more advanced case there was a decrease of nucleo-protein which might be associated with the disappearance of the Nissl substance in the neurones, and an increase of simple protein corresponding to an increase of glia fibrils; also in both cases the lipoid sulphur and phosphorus showed a diminution, but the smallness of the size of the samples of brain matter used in that investigation made it necessary that further analyses should be made on larger samples before any conclusions could be based on the latter results.

Since that time the methods for the chemical investigation of the brain have been revised and elaborated² and the following research has been made on larger samples, using the methods in their amended form. The methods employed, with full analytical technique, have been already described² but it appears necessary to give a résumé of the scheme of analysis. By means of solvents the chemical constituents of the brain tissue are separated into four general groups: (1) lipoids, (2) extractives, (3) inorganic constituents, (4) proteins. The following scheme explains this separation:—

¹ *Archives of Neurology*, 1907, iii, p. 218.² *Archives of Neurology*, 1909, iv, p. 174.

The variations of the elements phosphorus and sulphur in these groups were investigated for the following reasons. Phosphorus is the radical which seems to play the rôle in the building up of the most complex constituents of the cell, the nucleins and phosphatids, and the variation in its distribution between these and the water-soluble forms should therefore give an indication of the amount of formation or destruction of these important cell constituents. Sulphur occurs in the body in varied stages of oxidation, and the variations in the different stages probably offer a means of estimating the extent to which oxidizing reactions are taking place in the tissues. Sulphur occurs as $-SH$ or cystin sulphur in proteins, as sulphonate or taurin like sulphur, as ethereal sulphates and inorganic sulphates; it enters the organism mainly as unoxidized or cystin sulphur and leaves in an oxidized form as inorganic sulphates.

The following forms of phosphorus and sulphur have been estimated in this investigation.

(1) *Lipoid Phosphorus*.—Phosphorus attached to the phosphatid molecules (lecithins, kephalins, sphingomyelin).

(2) *Extractive Phosphorus*.—Water-soluble inorganic and organic phosphorus compounds; previous experiments have tended to show that the water-soluble phosphorus compounds extracted from the protein fraction are mainly inorganic, but it is difficult to say how far the organic forms may not have been split up in the process of estimation.

(3) *Protein Phosphorus*.—Phosphorus in combination with proteins, nucleo-proteid.

(1) *Lipoid Sulphur*.—Sulphur in combination with lipoids; cannot be removed by cold dilute hydrochloric acid, but splits off as sulphates on prolonged boiling with dilute hydrochloric acid.

(2) *Neutral Sulphur*.—Does not split off as sulphuric acid on prolonged boiling with dilute hydrochloric acid. Does not form lead sulphide on treatment with alkali and lead acetate. Is not precipitated by phosphotungstic acid except to a very slight extent (about 5 per cent). Reacts with α naphthyl isocyanate like an amino acid, and represents therefore an intermediary state in the oxidation of cystin to sulphuric acid or ethereal sulphates, probably of the nature of taurin.

(3) *Inorganic Sulphur*.—Precipitated directly by barium chloride in acid solution. In this investigation the inorganic and neutral sulphur have been classed together as extractive sulphur, previous work having shown that the amounts of inorganic sulphur are so small that their investigation is a difficult matter.

(4) *Protein Sulphur*.—Sulphur in combination with proteins.

One hundred gramme samples of the minced whole brain from two cases of amaurotic idiocy, with a similar sample of the normal brain of a child of about the same age, have been investigated according to the above scheme, with the following results. Table I shows an approximation of the main groups of constituents of the brain tissue in percentage of total solids :—

TABLE I.

	Age 18 months Normal brain	Age 20 months Amaurotic idiocy Case III	Age 17 months Amaurotic idiocy Case IV
Simple protein ...	35.0	29.6	30.8
Nucleo-protein ...	10.3	13.7	10.0
Phosphatids ...	28.0	21.9	19.8
Cerebrins ...	13.9	15.9	12.2
Cholesterol ...	11.0	11.8	8.9
Extractives ...	Not estimated.		
Ash ...	Not estimated.		
Total phosphorus ...	1.503	1.357	1.318
Total sulphur ...	0.49	0.396	0.47
MOISTURE ...	81.52	83.44	79.31

The analysis made on 100 grm. samples of the uniformly minced brain confirm the results previously obtained from the analysis of smaller samples of the grey and white matter separately, that there is a decrease of the phosphatids in the brain of these cases, with a diminution of the total phosphorus and sulphur. The figures for the normal brain are in agreement with former analyses made on brain from children of about the same age with the exception that the nucleo-protein approximation is somewhat low.

The results of one of the cases previously reported showed a diminution of nucleo-protein with a corresponding increase of simple protein in the grey matter; this change is not apparent in the above cases in which uniform mixtures of the grey and white matter were analysed. This does not, however, negative the former result as the amount of phosphorus in the protein fraction is very small, and when the white matter (which has not been found deficient in nucleo-protein) is included, the departure from the normal is greatly increased, and unless it is very marked may be beyond the limits of chemical analysis. As further cases are obtainable this point will be further investigated on large samples of the grey matter separately.

Except in the case of phosphatids, the slight variations in the other constituents—cerebrins, cholesterol, &c.—may be explained as the result

52 Carlyll & Mott: *Seven Cases of Tay-Sachs Disease*

of nutritive changes. The above figures, however, are approximations of the general groups of constituents, and a more accurate idea of the chemical abnormalities met with in the pathological brains is shown by the following Table II giving the percentage distribution of the elements phosphorus and sulphur. Tables II and III show the distribution of phosphorus and sulphur in percentage of total phosphorus and sulphur.

TABLE II.

	Normal	Case III	Case IV
Protein phosphorus...	3.9	5.7	4.3
Lipoid ..	72.2	62.5	58.4
Extractive ..	23.7	31.7	37.2

TABLE III.

	Normal	Case III	Case IV
Protein sulphur	59.2	61.2	59.4
Lipoid ..	19.4	14.8	12.5
Extractive ..	21.4	24.0	28.1

The above table shows that there is a *marked relative diminution of the lipoid forms of phosphorus and sulphur with a corresponding increase of the extractive forms*, the protein and sulphur and phosphorus showing no marked change.

*Motor Localisation in the Brain of the Gibbon, correlated with a
Histological Examination.**

By F. W. MOTT, EDGAR SCHUSTER, and C. S. SHERRINGTON.

(Communicated by Prof. C. S. Sherrington, F.R.S. Received March 28,—
Read May 4, 1911.)

Motor localisation in the Gibbon has not been hitherto determined experimentally, probably owing to the difficulty of obtaining a suitable animal. It appeared to be desirable, therefore, to see whether the habits and mode of life of this animal could be correlated with an increased development of the motor cortex. One of us (F. W. M.) had some years ago, by a comparative study of the convolutional pattern of the brains of Lemurs and Apes, made the following deduction:† “The remarkable use this animal makes of its arms and hands can be correlated with a remarkable expansion of the cortex in the precentral region, as shown by the development of a broad gyrus extending from the middle of the precentral region to form the second frontal convolution. Now if we turn to the Ape’s brain (*Macacus*), and see what the effect of this development would be, we observe that it would push forwards and downwards that portion of the cortex which on stimulation gives rise to movement of the head and eyes, particularly that which gives rise to eye movements, etc.” Figures were shown to indicate that the sulcus arcuatus would be pushed down to join the sulcus rectus. The following experiments by stimulation, correlated with a complete histological examination of the cortex in front of the central sulcus, have confirmed this deduction.

The animal used for the experiments was a male and black in colour; it was remarkably agile; when standing or running on the ground it maintained almost an erect posture, using its long arms to balance itself very much as a man would walk on a tight rope with a balancing-pole. It was kept for some days before the experiment in the animal room of the Physiological Laboratory, Liverpool, and it was frequently heard to utter vocal sounds of very varying pitch and quality. Thus it could imitate the shrill high-pitched whistles of the guinea-pig and the relatively low-pitched bark of the dog. A short account of the larynx of this animal will be made the subject of a future publication.

* A portion of the expense of this research has been defrayed by a Government Grant from the Royal Society.

† “On the Physiological Significance of the Convolutional Pattern in the Primates,” ‘Brit. Med. Journ.,’ 1906.

DETAILS OF THE EXPERIMENTS.

The animal was anaesthetised with chloroform and ether, and a light degree of anaesthesia maintained after the brain had been exposed.

The accompanying protocol describes the results obtained, and fig. 1 L and R indicate the points of stimulation.

PROTOCOL OF EXPERIMENTS.

Left Hemisphere.

Unipolar stimulation: diffuse electrode on R. foot; small electrode (ball-pointed, ball about 0.5 mm. diameter); stimulus in Kronecker units (K.U.):—

500 K.U.—

1. Movements of nostril.
2. Retraction of lip, opening of jaw.
3. Turning of head to opposite side.
4. Extension of elbow.
5. Ditto and movement of thumb.

600 K.U. (large electrode with ring loop for application, 4 mm. in diameter)—

6. Flexion of elbow, some retraction of shoulder.
7. Closure of eyelids.
8. Inward rotation of wrist, reaching forward movement from shoulder.
- 8 (again). Drawing-back movement.
- 6 (again). Flexion of elbow, drawing-to of shoulder.
- 8 (again). Drop (flexion) of wrist.
9. Extension of shoulder.
10. Extension of shoulder, accompanied by abduction of wrist, extension of fingers, with a little abduction of thumb (also relaxation of biceps).
11. Elevation of shoulder.
12. Slight flexion of knee.

Bipolar stimulation (stimulus value in centimetres):—

9 cm.—

13. Wrinkling of forehead.
14. Closure of lower and upper eyelids.
15. Forehead and nostril.

Unipolar stimulation: diffuse electrode on L. foot; loop electrode as before:—

600 K.U.—

16. Flexion of hip.
17. Flexion of knee and extension of toes and hallux (succeeded by flexion).
- 17 (again). Flexion of knee, extension of ankle and toes, going back into flexion.
- 17 (again). Flexion of hip and knee, extension of foot and toes.
18. Slight flexion of toes (without hallux), extension of ankle with some opening (i.e. separation) of toes.

Bipolar stimulation as before:—

18. (again). Slight contraction of toes.

Unipolar stimulation with fine ball-pointed electrode:—

- 17 (again). Extension of hip and knee, abduction of leg.
- 17 (again). Abduction.
19. Extension of foot (very slight).

20. Distinct flexion of hip and knee, flexion of toes.
 20 (again). Flexion of knee, flexion of hip.
 21. Mouth.
 22. Retraction of tongue.
 22 (repeated). Same results. ($\frac{1}{2}$ cm. of cortex for tongue.)
- 1000 K.U.—
 23. Eyeballs turned inwards and downwards.
 24. Upward movement of eyeball.
 23 (again). Eyeballs turned downwards and slightly inwards.
 23 (repeated). Same results.
- 1250 K.U.—
 Eyes. No result.
Bipolar stimulation :—
 9 cm. No result.
 8 cm. Mouth moves.
Unipolar stimulation as before :—
- 1250 K.U.—
 22a. Movement of tongue (protrusion of opposite side).
 22b (at lowest point). Movement of tip of tongue.
 25. Here a very slight movement of tongue tip was obtained from just behind inferior extremity of central fissure, tip of tongue deviated to opposite side (but see below).
Unipolar stimulation : small electrode :—
- 800 K.U.—
 22a. In front of fissure, deviations of tongue as before.
 25. And various other points behind fissure, nothing.
- 1250 K.U.—
 22a-b. Well-marked protrusion and deviation to opposite side.
 22a-b (again). Protrusion, obtained repeatedly.
 22a-b (again). Retraction.
 25. Nothing.
 25 (again). Nothing (repeated).
 (Results obtained above from 25 with large electrode attributed to diffusion.)
- Right Hemisphere.*
- Unipolar stimulation* : coarser electrode :—
- 800 K.U.—
 1. Extension of wrist, opening of fingers.
 2. Extension of elbow and wrist, flexion of fingers.
 3. Flexion of fingers, chiefly index, abduction of thumb.
 4. Movements of wrist, tendency to pronation.
 5. Extension of fingers, hallux, wrist ; some abduction and tendency to pronation.
 6. Eye-movements, outward and upward.
- 900 K.U.—
 7. Extension of wrist.
- 1000 K.U.—
 3 (again). Flexion of fingers and wrist (clenching of hand).
 (Interval of 20 minutes ; stimulation then resumed.)

As before, but with fine electrode :—

900 K.U.—

8. Primary eversion of foot, followed by inversion ; movements of hip and knee.
- 8 (again). Slight eversion, then inversion.
9. Slight flexion of hip and knee, movements of trunk (pelvis raised).
- 8 (again). Movements of trunk, flexion of hip and knee, dorsal flexion of foot.
- 8 (again). Extension of foot.
- 9 (again). Marked extension of foot and extension of knee.

Left Hemisphere.

1000 K.U.—

- 19a. Dorsal flexion of (right) foot, flexion of (right) hip and knee (walking movements).
- 19b. As before ; more definite.

Calcarine Region. (Both Hemispheres.)

Bipolar stimulation : distance between points widened to 6 mm. :—

8 cm.—

1. Left hemisphere, just above polar end of calcarine ; slight movement of eyeball upwards and to left.
- 2 (repeated). Movement of eyeball upwards and a little inwards.
3. Right hemisphere, corresponding point to 1 ; movement of eyeball over to left in wavering manner.

6 cm.—

4. Right hemisphere, mesial surface of pole ; movement of eyeball over to left, and somewhat downwards, dilation.
5. Right hemisphere, outer surface (polar region) ; same result.
6. Left hemisphere, similar point to 5 ; eyes move to right.
7. Left hemisphere, at anterior extremity of external calcarine ; same result.

Larynx.

Left Hemisphere.—Bipolar stimulation : wide electrodes :—

6 cm.—

26. Adduction of chords.
- 26 (repeated). Same results.
- 26 (again). Adduction of both chords, but chiefly same side.

Bipolar stimulation (C. S. S. stimulating) :—

5 cm.—

26. Slight adduction.
- 26a. Same as 26.

The stimulation of the calcarine region of the occipital lobe was not performed until the motor area had been mapped out, consequently the cortex may not have been in such a favourable condition for excitation. Unipolar excitation gave no definite results ; the stimulation so given may not have been diffuse enough. Bipolar excitation invariably produced deviation of the eyes away from the hemisphere stimulated when one pole was placed above and the other below the calcarine fissure ; the regions stimulated extended from the mesial surface of the pole of the occipital

lobe along the external surface to the anterior extremity. The electrodes placed elsewhere on the occipital lobe gave no movements. It may therefore be inferred that owing to the infolding of the cortex to form the fissure stimulation of this region by bipolar excitation extended to a sufficient number of motor neurones, or that it is in this region indicated in fig. 1 R by area 28 that the optic radiations terminate in greater numbers than elsewhere in the occipital lobe.

Again, it is probable that unilateral stimulation was inefficient in the production of adduction of the vocal chord, because this experiment was the last performed. Definite movements were obtained for a short time, however, by bipolar stimulation of the region 26 indicated; later on, however, the same strength of stimulus failed to give any response, and the animal was killed.

It is of interest to note that unipolar stimulation gave no result when applied to the ascending parietal convolution; this fact, as we shall see, accords completely with the histological observations.

HISTOLOGICAL OBSERVATIONS.

At the close of the experiments, after the animal had been killed, the brain was hardened *in situ* by an injection of formalin solution through the carotid artery. It was thought that in this way the structure of the cells would be best preserved. Subsequent examination showed that this anticipation was not realised, for the preservation was not sufficiently good to make a complete survey of the cell lamination of the whole brain profitable. It was, however, quite adequate for the purpose of determining the extent of the principal areas in the lateral and mesial surfaces of the frontal lobe. For this purpose the brain was divided into blocks, arranged in such a way as to avoid, as far as possible, the necessity of cutting any part of the cortex obliquely or tangentially, and the planes of section were plotted carefully on outline drawings of the surface of the hemispheres. After the blocks had also been drawn, they were embedded in paraffin in the usual way, and cut into sections parallel to their faces. The sections were stained with polychromé methylene blue.

Both hemispheres were examined, but the results have been mapped only on the drawings of the right hemisphere (figs. 2 and 3). Since the types of cortex here dealt with have been often and fully described and figured, and since their structure in this case presents apparently no unusual features, special descriptions or drawings have not been given.

Figs. 2 and 3 show the distribution of two quite distinct types of cortex in the lateral surface of the Gibbon's brain. That portion which is

marked in the diagram with a number of large and small dots is covered by a type of cortex characterised by the absence of a distinct layer of "granules" or "stellate cells," and thus corresponding to Campbell's* precentral and

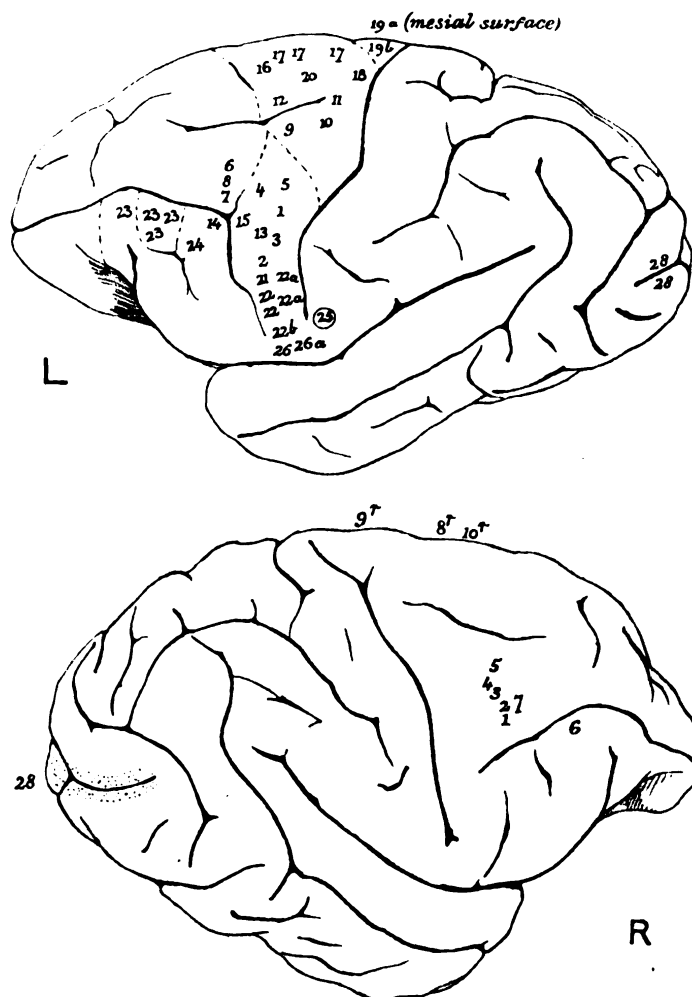


FIG. 1.

L, Lateral Surface of Right Hemisphere; R, Mesial Surface of Right Hemisphere.

intermediate precentral types, or to Brodmann's† types 4 and 6. The size of the dots shows roughly the relative size of the largest cells in the ganglionic layer or inner layer of large pyramids. The largest of these dots indicate the presence of cells which may safely be called giant pyramids or Betz

* Campbell, 'Histological Studies on the Localisation of Cerebral Function,' Cambridge, 1905.

† Brodmann, "Beiträge zur histologischen Lokalisation der Grosshirnrinde," III, 'Journal für Psychologie und Neurologie,' 1905, bd. 4, heft 5—6.

cells; their position thus marks the extent of Campbell's precentral or motor area, or of Brodmann's type 4. The extent of the intermediate precentral cortex of the former, or type 6 of the latter, is shown by the smaller dots. The Betz cells are most numerous, largest, and cover a wider zone on the mesial surface of the hemisphere above the sulcus cinguli and on the lateral

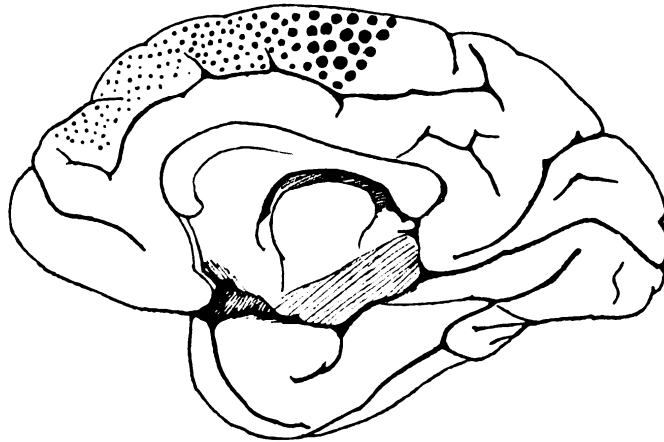


FIG. 2.

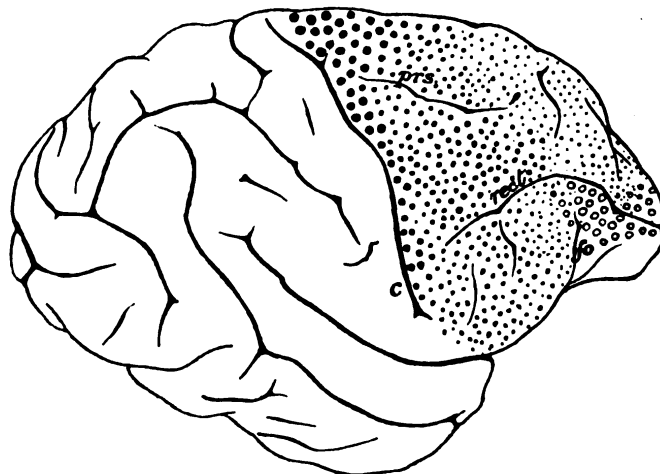


FIG. 3.

prs., Sulcus precentralis superior. *rect.*, Sulcus rectus. *fo.*, Sulcus fronto-orbitalis.
c., Sulcus centralis.

The black dots in the above figures indicate the area covered by the precentral (motor) and intermediate precentral types of cortex; the circles the granular frontal type of cortex.

surface in the neighbourhood of the supero-mesial border (fig. 3). On the lateral surface, below the level of the sulcus precentralis superior (*prs.*), they are confined to the anterior wall of the sulcus centralis and to a narrow strip of the ascending frontal convolution lying immediately in front of that fissure.

It will be seen on comparing these figures with Campbell's diagrams of the brains of the Orang and Chimpanzee, that the distribution of the Betz cells is very similar in all three cases. The Gibbon presents perhaps a slightly closer resemblance to the Orang in this respect than to the Chimpanzee.

It is the distribution of the intermediate precentral area which forms the most characteristic feature of the Gibbon's brain. The great forward extension of this area distinguishes it in a very striking way from the Orang and Chimpanzee, on the one hand, and Cercopithecus and the Baboon on the other. This extension is most marked in the region which may be described as the middle frontal convolution, namely, that portion of the lateral surface which lies between the sulcus precentralis superior (*prs.*) above, and the sulcus rectus (*rect.*) below. The area occupied by the granular frontal cortex (Campbell's frontal cortex and Brodmann's type 9) becomes in this way very much restricted, and above the sulcus rectus it occupies only the very small space in the neighbourhood of the frontal pole indicated in fig. 3 by small circles. Below that fissure the layer of granules or stellate cells is well developed in nearly the whole region lying in front of the fronto-orbital sulcus (*fo.*).

Probably as a result of the great development of the intermediate precentral area the sulcus arcuatus, the upper limit of which in Cercopithecus and the Baboon arches round the posterior end of the sulcus rectus, and lies just within or actually forms a boundary to this area, has been pushed downwards to such an extent that it has become continuous with that fissure. This condition can be recognised most clearly in the left hemisphere, where the sulcus rectus has posteriorly a well developed downwardly directed limb, which is clearly the homologue of the lower portion of the sulcus arcuatus; in the right hemisphere it is very difficult to recognise the latter at all.

Another point worthy of attention is that in the cortex of the posterior part of the middle frontal gyrus the large cells of the ganglionic layer, or inner layer of large pyramids, are somewhat larger than in the region lying above the anterior end of the sulcus precentralis superior, or below the sulcus rectus, but are not nearly so large as those which have previously been referred to as unquestionable giant pyramids.

[Reprinted from the PROCEEDINGS OF THE ROYAL SOCIETY OF MEDICINE,
February, 1911.]

**The Incidence of Gall-stones and of Primary Carcinoma of the
Gall-bladder and Biliary Passages in the Insane.**

By J. P. CANDLER.¹

THE following paper is based upon the investigation of 2,228 autopsies conducted at the London County Asylum, Claybury, during the past ten years. The main points to which attention has been directed have been the investigation of the incidence of gall-stones, and the prevalence of primary carcinoma of the gall-bladder and biliary passages in the series of cases examined. The investigation was commenced at the suggestion of Dr. Mott who, while aware of the frequency with which gall-stones are found on the post-mortem table at Claybury, could not recall to mind meeting with a case of primary carcinoma of the gall-bladder. By reason, therefore, of the importance which is assigned to gall-stones in the causation of primary carcinoma of this organ, he considered that an investigation on these lines might yield some points of interest.

The Incidence of Gall-stones.—The total number of autopsies investigated was 2,228; of these 1,169 were females, and 1,059 males. Gall-stones were found in 315, a percentage for both sexes of 14·13. Of the 1,169 females there were 210 cases with gall-stones (17·85 per cent.), and of the 1,059 males, 105 cases (9·91 per cent.).

¹ From the Pathological Laboratory of the London County Asylums.

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Reference to Hospital Statistics.—Dr. Hale White estimates from post-mortem records on Europeans of all ages, and of both sexes that gall-stones are present in from 5 to 10 per cent. Rolleston estimates the percentage incidence in post-mortem examinations to be between 6 and 10. Schroeder has found in Strasburg a percentage incidence of 12 for both sexes. In his cases the proportion of female cases was 20 per cent., against 4·4 per cent. of males, an incidence for females in considerable excess of that obtained at Claybury.

Dr. Ticehurst¹ gives the following table on the incidence of gall-stones taken from the papers of Naunyn and Kelynack :—

TABLE I.					
Observer			Place of observation		Percentage incidence of gall-stones
Poulson	Copenhagen	...	3·8
Peters	Kiel	...	5·0
Munk	}	...	Munich (10 years)	...	6·2
Rother					
Hiller					
Brockbank	Manchester (487 cases)	...	6·5
Fielder	Dresden	...	7·0
Schloth	Erlanger (24 years)	...	7·2
Voelcker	286 cases	...	9·4
Roth	Basle	...	10·0
Frank	Vienna	...	10·0
Schroeder	Strasburg (7 years)	...	12·0

Ticehurst, in his investigation based upon the post-mortem records of Guy's Hospital for twenty-five years (1876-1900), found 333 cases of gall-stones in 11,031 autopsies, a percentage of 2·08, or excluding patients dying under 20 years of age, 6·3 per cent.

From the figures above given it would appear that the incidence of gall-stones among the insane was greater than that found in ordinary hospital practice, to which fact attention has already been drawn by Dr. Beadles, who at Colney Hatch Asylum found gall-stones present in 27 per cent. of the female cases, and in 5 per cent. of the males. Beadles quotes Warnock's figures of 50 per cent. in females, and 11 per cent. in males dying in Peckham House Asylum (Private), to show that this excess is by no means confined to pauper lunatics.

The figures from Claybury appear to bear out this contention, but not so markedly as those of Beadles and Warnock; nevertheless, it is probable, from the evidence obtainable, that the percentage incidence of gall-stones is slightly higher among the insane than among the general

¹ "On the Mortality from Gall-stones." Thesis for M.B. Degree, Cantab. 1908.

population. The greater incidence at Colney Hatch may be due to the fact that it is the second oldest London County Asylum, and probably the average age of the inmates is higher than that of Claybury, which is comparatively a new asylum. Reference to Table II, compiled from the Claybury statistics, shows that, with the exception of the age-period 40—50 years, there is a gradual increase in the percentage incidence of gall-stones as age advances, and this percentage agrees fairly accurately with that given by Schroeder.

TABLE II.

Age-periods	Total number of autopsies	Number of cases with gall-stones	Percentage	Schroeder's percentage
0 to 20	16	0	0	2·4
20 „ 30	155	6	3·87	3·2
30 „ 40	375	31	8·26	11·5
40 „ 50	424	27	6·36	11·1
50 „ 60	412	54	13·1	9·9
60 „ 70	440	85	19·31	—
70 „ 80	337	90	26·70	—
80	69	22	31·83	—
60 and over	846	197	23·28	25·2

The figures which I have recorded give the incidence of the gall-stones as regard hospital patients and the insane. It is of importance to compare the statistics afforded by these two classes, and to ascertain how far the figures can be used as an indication of the incidence of these affections among a general population.

The preceding tables show that the incidence of gall-stones among hospital patients varies considerably in the hands of different observers. No satisfactory conclusions can be given to account for these variations from a mere perusal of the figures, unless it be known that the statistics have been compiled under precisely similar conditions, especially as regards the number of cases dying at the various age-periods, the percentage incidence of gall-stones at these age-periods, and the number of cases dying before the age of 20. This last factor is of the utmost importance, for since gall-stones are exceedingly rare in cases dying before the age of 20, the inclusion of a large number of such cases before age 20 will materially affect the tables. This is well shown by the figures of Ticehurst—the percentage incidence of gall-stones on 11,031 autopsies was only 2·08; of these no less than 3,156 were under 20 years of age, and only one case with gall-stones was found amongst this number. The elimination of all cases dying before 20 increased the percentage incidence to 6·3.

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The percentage incidence of gall-stones at Claybury Asylum was 14·13 on 2,228 autopsies. The number of cases dying under 20 years of age was only 16, and in none of these cases were gall-stones found.

There is a considerable difference between the incidence of gall-stones among the insane (as shown by the Claybury statistics and elsewhere) and that among hospital cases. Even after the elimination of all cases dying before 20 years of age, there is still a great difference between the Claybury figures and those from Guy's Hospital. The following table shows the total number of gall-stones found at the different age-periods at the two institutions :—

TABLE III.

Age-period	Number of gall-stones	
	Guy's Hospital	Claybury Asylum
10 to 20	1	0
21 „ 30	11	6
31 „ 40	36	31
41 „ 50	85	27
51 „ 60	91	54
61 and over	107	197

This table shows that out of an approximately equal number of cases with gall-stones, the Claybury figures provide a smaller number at age-periods 40—50 and 50—60, and a considerably greater number at 60 years and over, than at Guy's. I have been unable to obtain the number of cases dying at the different age-periods at Guy's for comparison with the Claybury figures, and, in the absence of these, I hesitate to form any definite conclusions. As, however, the incidence of gall-stones increases with advancing age, the inference is that a relatively greater number of deaths occurred at Guy's Hospital between the ages 40—60 and less from 60 onwards than occurred at Claybury Asylum.

Mayo Robson has suggested that the incidence of gall-stones among hospital patients is less than that in a general population because hospitals are patronized by the labouring classes, in whom the incidence of gall-stones is less. This may be so, but I am inclined to think that there is another explanation which may account for any lessened incidence of gall-stones in the hospital statistics, namely, that a relatively small number of the aged poor seek hospital assistance, but die from old age in their own beds or in the infirmaries, and thus fail to provide the hospitals with the necessary material for complete statistics.

Statistics obtained from asylums (at any rate as far as the relative

incidence of gall-stones is concerned) would be more comparable with those obtained from a general population from which all cases dying before the age of 20 have been eliminated, by virtue of the fact that the population of asylums is not constantly changing as is that of hospitals. The patients are admitted solely for their mental condition, irrespective of any bodily ailments, and many of them on admission are in good health and ultimately die of senile decay after many years of residence in the asylum. They therefore provide a greater number of people in the later years of life than do hospitals. In the Claybury statistics, out of 2,228 autopsies, 1,258, or 56 per cent., had survived the age of 60; 406, or 18 per cent., survived the age of 70; and 69, or 3 per cent., survived the age of 80.

The death-rate in asylums differs from that in a general population in that there is a greater mortality in the mid-period of life from phthisis, general paralysis of the insane, pneumonia, and dysentery. The average duration of life, therefore, among the insane is probably shorter than among the general population who have survived the age of 20: and this should tend to *diminish* the relative incidence of gall-stones among the insane. But, in spite of this, the percentage incidence in the insane is estimated to be *higher* than in a general population. Various explanations have been put forward to account for this increased incidence in the insane, such as the greater prevalence of gastric disorders, of constipation, of melancholia and lethargic states, and of the breaking down of nervous tissue with a greater deposition of cholesterol in the bodily tissues. Thudichum, commenting upon the paper of Beadles, regarded the high percentage of persons dying in asylums with gall-stones as being evidence of some causal relationship to cerebral decay and insanity. No doubt this great authority on the chemistry of the brain considered the brain decay and resulting cholesterol production accountable for the higher incidence of gall-stones among the insane than among the general population.

The Incidence of Primary Carcinoma of the Gall-bladder and Biliary Passages as ascertained at Guy's Hospital.—Ticehurst found in 11,031 autopsies, with 333 cases of gall-stones, that there were 45 cases of primary carcinoma of the gall-bladder (13·5 per cent.), and 15 cases of primary carcinoma of the bile-ducts (4·5 per cent.), or, combining the two, a total of 60 cases of primary carcinoma of the gall-bladder and biliary passages (18 per cent.).

The Incidence of Primary Carcinoma of the Gall-bladder and Biliary Passages in the Insane.—Of the 2,228 cases examined at Claybury 315

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were found to have gall-stones. In this series there were only two definite cases of primary carcinoma of the gall-bladder (one male and one female), gall-stones being found in the gall-bladder in each case. In other words, the incidence of primary carcinoma of the gall-bladder was 1 in 1,000 of the insane dying at Claybury during ten years; or, looked at from the percentage incidence of gall-stones, two cases of primary carcinoma of the gall-bladder out of 315 cases of gall-stones (0·65 per cent.). Both these cases were proved by microscopic examination. In addition to these two cases there was one case which occurred at the commencement of the series which was noted as (?) primary carcinoma of the gall-bladder, or primary malignant disease of the breast with secondary involvement of the liver and gall-bladder. The right breast had been previously amputated, and there was a malignant mass in the site of the scar. The liver was studded with malignant nodules. The gall-bladder was involved in a mass of cancer and contained one large stone the size of a pigeon's egg. The case was not microscopied. Even if this be conceded as a case of primary malignant disease of the gall-bladder, which is very doubtful, the percentage incidence is only 0·95.

Of primary carcinoma of the liver and biliary ducts apart from the gall-bladder there were only three very doubtful cases occurring very early in the series. In Case I, the growth in the liver was probably secondary to malignant disease of the ovary. In Case II it was probably secondary to carcinoma originating in the pylorus; and in Case III it was noted as probably secondary to primary malignant disease of the mediastinum. The gall-bladder was quite free from growth in each case, and there were no stones found either in the ducts or gall-bladder, nor any evidence of partial or complete destruction of the ducts by cicatricial contraction, consequent upon the previous passage of gall-stones along the ducts. These cases were not microscopied. Even if they be included as possible instances of primary carcinoma of the bile-ducts consequent upon irritation of stones which had ultimately been passed into the intestine, the percentage incidence in relation to gall-stones is only 0·95.

It will thus be seen (*vide* Table IV) that the percentage incidence of primary carcinoma of the gall-bladder and biliary passages in the insane, as afforded by the Claybury figures, is markedly less than the hospital percentage incidence. As the incidence of these diseases among a general population is based upon hospital statistics, such a wide variation between the Guy's Hospital figures and those of Claybury requires some comment, especially as gall-stones are considered to play so important a part

in the production of primary carcinoma of the gall-bladder and biliary passages.

Opinions as to the Rôle played by Gall-stones in the Causation of Primary Malignant Disease of the Gall-bladder.—The opinion of those who have studied this subject is almost entirely in agreement—namely, that gall-stones are a cause of primary malignant disease of the gall-bladder and ducts, especially of the former.

Dr. Hale White, quoting from Ticehurst's figures, states that the latter found among the 11,031 autopsies at Guy's Hospital (in which there were 333 cases of gall-stones) 45 examples of primary carcinoma

TABLE IV.—SHOWING A COMPARISON OF THE INCIDENCE OF GALL-STONES AND PRIMARY CARCINOMA OF THE GALL-BLADDER AND BILIARY PASSAGES IN CASES DYING AT CLAYBURY ASYLUM AND GUY'S HOSPITAL.

	Total No. of autopsies	Total No. with gall-stones	Percentage incidence of gall-stones	No. of autopsies over 20	Percentage incidence of gall-stones over 20	No. of cases of primary carcinoma of gall-bladder	Percentage	No. of cases of primary carcinoma of bile-ducts	Percentage	No. of cases of primary carcinoma of gall- bladder and bile-ducts	Percentage
Guy's Hospital	11,031	333	2·08	7,875	6·3	45	13·5	15	4·5	60	18·0
Claybury Asylum	2,228	315	14·13	2,212	14·24	2 1?	0·65 0·95?	0 3?	0 0·95?	2 4?	0·65 1·9?

of the gall-bladder, and in 43 of these, or 95 per cent., gall-stones were present; and there were 15 cases of primary carcinoma of the bile-ducts, and gall-stones were present in 11, or 75 per cent. Hale White concludes that about 20 per cent. of those who have gall-stones subsequently suffer from malignant disease of the biliary passages. He further emphasizes that this is not as widely understood as it should be, the chief reason being that most cases of malignant disease of the biliary passages are called malignant disease of the liver, and hence the causative importance of the gall-stones is missed.

Moynihan states that one of the most serious sequelæ of cholelithiasis is malignant disease of the gall-bladder or ducts, and that the close connexion between gall-stones and malignant disease has never lacked recognition.

Mayo Robson, on the other hand, states that cancer of the gall-bladder is by no means frequent, and as a primary affection is somewhat rare. It is usually due to the irritation of gall-stones or to extension from adjoining organs.

Rolleston writes that special interest is attached to the association of gall-stones and carcinoma of the gall-bladder—Musser, 69 per cent.; Courvoisier, 91 per cent.; Siegert, 95 per cent.; Fütterer, 70 per cent.; Winton, 81 per cent.; Zenker, 85 per cent. Conversely, it appears that primary carcinoma of the gall-bladder occurs in from 14 to 4 per cent. of all cases of cholelithiasis.

Schroeder estimated that 14 per cent. of persons with cholelithiasis eventually became the subjects of carcinoma of the gall-bladder.

In 149 cases of gall-stones, abstracted from the records of Guy's Hospital by Keay, there were 17 cases of carcinoma of the gall-bladder or cystic duct, equivalent to 11.4 per cent.

Riedel estimates the percentage of primary carcinoma in cholelithiasis to be from 7 to 8 per cent.

Among 242 cases of gall-stones at St. George's Hospital there were 10 cases of primary carcinoma of the gall-bladder, or 4.1 per cent.

Rolleston sums up by saying that "gall-stones are present in the great majority of cases of primary malignant disease of the gall-bladder, while carcinoma develops in 14 to 4 per cent. of cases of cholelithiasis."

The evidence, therefore, shows that gall-stones are present in practically 80 to 90 per cent. of all cases dying from primary carcinoma of the gall-bladder, while it has been remarked by Ticehurst and others that gall-stones are rarely found when the biliary passages are affected by growth secondary to that elsewhere. So far as the Claybury statistics show they confirm Ticehurst's statement. Both cases of primary carcinoma of the gall-bladder contained calculi, while cases in which the liver was affected with growth secondary to malignant disease commencing in some other organ showed little or no excess in the incidence of gall-stones.

The point, however, to which I desire to draw attention, is as to whether the association between gall-stones and primary malignant disease of the gall-bladder is so frequent as to justify the opinion that because calculi are found in 90 per cent. of cases of primary carcinoma of the gall-bladder they are to be looked upon as so potent a factor in the causation of this disease. On the one hand we have statements to show that no less than 20 to 18 per cent. (Hale White and Ticehurst) and 14 to 4 per cent. (Rolleston) of cases of cholelithiasis succumb to

malignant disease of the gall-bladder and ducts. On the other hand, Mayo Robson states that cancer of the gall-bladder is by no means frequent, and as a primary affection is somewhat rare. These two statements are diametrically opposed. The estimates of Hale White, Ticehurst, and Rolleston are based on hospital statistics. They cannot, in my opinion, be taken to represent the incidence among the general population. They are based on selected cases among the general population, who, on account of symptoms arising from the onset of carcinoma, seek hospital advice. The inclusion of these cases will at once increase the incidence of carcinoma of the gall-bladder in relation to gall-stones and upset the balance of comparison with that of a general population. The incidence of carcinoma in a general hospital could not be taken as indicative of the prevalence of this disease in a general population, nor could the incidence of lung affections among the insane be used to indicate the frequency of these conditions among the sane.

If we take Hale White's estimate (*viz.*, that about 20 per cent. of cases of gall-stones ultimately develop primary carcinoma of the gall-bladder and biliary passages) and apply it to the Claybury statistics, then out of the 315 cases there should have been as many as 60 cases of primary malignant disease of these regions, or assuming that 10 per cent. of a general population surviving the age of 20 suffer from gall-stones, then two out of every 100 persons should develop primary carcinoma—a supposition which I think is not justified. It may be suggested that the smaller incidence of primary carcinoma among the insane is due to the fact that their average age at death is lower than the average age at death of a general population surviving the age of 20. If all the cases of gall-stones dying before the age of 60 be eliminated from the Claybury statistics, there still remain 197 cases of gall-stones occurring from the age of 60 upwards. If Hale White's estimate be applied to these cases only, there should have been close on 40 cases of primary carcinoma of the gall-bladder in the Claybury statistics.

It is not my intention to discuss the various theories as to how gall-stones act in producing carcinoma of the gall-bladder, or as to whether gall-stones precede or are formed after the commencement of malignant disease of that organ; there is probably truth in both suppositions. If, as Mignot believes from experimental researches, a stratified well-formed biliary calculus can be formed in six months, it seems quite possible that a calculus could be formed as the result of changes set up in the mucous membrane by the onset of carcinoma before operation on, or death of, the patient.

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From the evidence obtained from the post-mortem statistics at Claybury Asylum I am, however, inclined to the opinion that the incidence of primary carcinoma of the gall-bladder and biliary passages in its relation to gall-stones among the general population is by no means so great as hospital statistics would lead us to believe, and that consequently there is not sufficient justification for assigning to gall-stones so important a rôle in the production of primary malignant disease of the gall-bladder and ducts.

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